





# FRONTISPIECE A

1	<i>Entamoeba histolytica</i>	} $\times 1,000$	17	<i>Enterobius vermicularis</i> $\times 350$
2	<i>Entamoeba histolytica</i> cyst, in saline		18	<i>Gastrodiscoides hominis</i> $\times 275$
3	<i>Entamoeba histolytica</i> cyst; iodine stained.		19	<i>Schistosoma mansoni</i> $\times 200$
4	<i>Entamoeba coli</i> .		20	<i>Schistosoma hematobium</i> $\times 200$
5	<i>Entamoeba coli</i> cyst; in saline		21	<i>Echinococcus</i> $\times 7$
6	<i>Entamoeba coli</i> 4-nucleated cyst iodine stained		22	<i>Aedes aegypti</i> $\times 8$
7	<i>Trichomonas hominis</i>		23	<i>Glossina palpalis</i> $\times 2$
8	<i>Giardia</i>		24	<i>Phlebotomus papatasi</i>
9	<i>Giardia</i> cyst		25	<i>Phlebotomus argentipes</i> } $\times 6$
10a	<i>Microfilaria</i> of <i>Wuchereria bancrofti</i>		26	<i>Pediculus humanus</i> $\times 8$
10b	<i>Microfilaria</i> of <i>Wuchereria malayi</i>	} $\times 625$	27	<i>Dermacentor andersoni</i> $\times 6$
11	Hookworm ova		28	<i>Trombicula alanyensis</i> adult $\times 8$ (Nymph inset)
12	<i>Ascaris</i> ova (fertilized)		29	<i>Xenopsylla cheopis</i> $\times 8$
13	<i>Ascaris</i> ova (unfertilized)		(Actual size of insects inset in ring)	
14	<i>Trichuris trichiura</i> ( <i>Trichocephalus trichiurus</i> )			
15	<i>Tenia saginata</i>			
16	<i>Fasciolopsis buski</i>			

The approximate magnification of each figure is shown



FRONTISPIECE B  
(Giemsa's stain  $\times 2,000$ )

- A Benign tertian (*Plasmodium vivax*)  
Young ring form, amœboid trophozoite, three-quarter-grown trophozoite, developing schizont, dividing schizont, male gametocyte, and female gametocyte
- B Malignant tertian (*P. falciparum*)  
Young ring form, four ring forms, including one secolé form, in one red cell, band form, a larger ring form with Maurer's dots, mature schizont, or rosette, male crescent, and female crescent
- C Quartan (*P. malariae*)  
Young ring form, young band form, large band form, schizont, merozoites (free), male gametocyte, and female gametocyte
- D (*P. ovale*)  
Young ring form, band form, two schizonts in one corpuscle, infected corpuscle showing a fimbriated outline, dividing schizont, male gametocyte; and female gametocyte
- E Trypanosomes  
(a) *T. gambiense* (b) *T. brucei* (c) *T. cruzi*
- F Bartonella
- G *Spirillum minus*
- H *Treponema recurrentis*
- I Leishmanias  
(a) 'Round' forms (Leishman Donovan bodies) from spleen puncture  
(b) 'Torpedo' forms of Leishman Donovan bodies  
(c) The flagellate forms
- J *Leptospira icterohæmorrhagiae* (the rope-like spirals would not show in a Giemsa-stained specimen)
- K Comma bacilli

# THE PRINCIPLES AND PRACTICE OF TROPICAL MEDICINE

BY

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1946

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THE MACMILLAN COMPANY · NEW YORK

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Published 1916

## PREFACE

The writer has attempted to give an accurate and concise account of the more important tropical diseases from the points of view of epidemiology and

as men- anæmia in the tropics and snakes and snake bite. He hopes that the book will be useful to the student, the practitioner and the public health worker and that it will be looked upon rather as a textbook than as a book of reference. For this reason he has not attempted to follow that mirage of completeness either as regards the individual subjects or the field of g the presenta- ited to exercise appear to him to

question that is discussed in the text of this book (see p. 3). No very satisfactory answer is given. However, the writer still had to decide what he was to include in the book and although he followed a preconceived plan, he admits that many of his decisions are impossible to defend on logical grounds and that some are difficult to uphold on any grounds.

Perhaps the most glaring omissions are two infectious diseases which are of very great importance in the tropics, namely smallpox and typhoid fever. These diseases are of course not confined to the tropics—but this is true of many other diseases included in the book—nor do they present any very special features in the tropics. It is true that the mild form of smallpox, *alastrim*, occurs in many tropical countries and provides a degree of protection to the population against infection by the more virulent strains of the virus. This form of the disease has seldom been recognized in India where in some recent years there have been nearly a hundred thousand smallpox deaths annually despite the extensive vaccination organization.

The immunity to typhoid fever, reputed to be enjoyed by some native populations in the tropics, is almost certainly a result of infection in childhood. With the advance of sanitation in India, for example, paradoxically the disease appears to be increasing especially in the adolescent and young adult groups of the middle class indigenous population. This apparent increase is probably the result of a higher rate of infection in the economically more important age groups. Typhoid is however, in the writer's experience, generally a milder disease in the tropics.

Both these diseases are well described in the ordinary textbooks of medicine and their omission is justified.

It is excused. In many tropical countries the disease is bid to oust malaria from its throne and sickness and although tuberculosis is a cosmopolitan disease its epidemiology, pathology and symptomatology certainly exhibit special features when it occurs in tropical populations. The only excuse the writer can offer is that our present state

of knowledge of tuberculosis in the tropics is not sufficiently standardized to make possible the preparation of a concise account of the subject, and he therefore felt that it would be better to omit it altogether.

Another obvious omission is a discussion on eye diseases and blindness in the tropics. This is a very important subject in which most practitioners in the tropics will sooner or later find themselves involved, but it is a specialist subject that appears to demand separate treatment.

In most books on tropical medicine considerable space is devoted to mycotic infections, sometimes—the writer feels—more than can logically be justified, although he himself has possibly erred too far in the other direction by omitting all reference to the systemic mycoses and only including those of the superficial mycoses that are common and particularly troublesome in the tropics.

Turning to errors of commission, one finds it difficult to justify the inclusion of tularæmia which is in no sense a tropical disease, though its modes of transmission are similar to those of several tropical diseases, it is however the usual practice to include tularæmia in books on tropical medicine and the writer has, perhaps somewhat weakly, fallen into line. Similar errors, not tropical, on the complete at

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laboratory work on a more extensive scale will require a laboratory handbook, such as Craig's *Laboratory Diagnosis of Protozoan Diseases* or the more comprehensive *Laboratory Methods of the United States Army* by Simmons and Gentzkow.

## LITERATURE

The writer would have been failing in his duty, if in writing this book he had not made free use of the existing textbooks of tropical medicine, especially Rogers and Megaw's *Tropical Medicine*, Manson Bahr's *Manson's Tropical Diseases*, Strong's *Stitt's Tropical Medicine*, and Craig and Faust's *Clinical Parasitology*. Scott's *History of Tropical Medicine* and the appropriate chapters in the *British Encyclopædia of Medical Practice* were also used freely. As for the periodicals, the special journals, the *American Journal of Tropical Medicine*, the *Transactions of the Royal Society of Tropical Medicine*, the *Annals of Tropical Medicine and Para-*

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course, above all, the comprehensive tropi-  
led the most useful material

## REFERENCES

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## PREFACE

workers freely by name without giving any supporting textual reference. This, the present writer has found a little irritating, and so he has the practice of referring to individual workers by name, perhaps frequently, but as far as possible giving the specific reference when mentioning a name. Repetition has been avoided as far as possible, when a reference is missing the reader should turn to an earlier chapter on a cognate subject. A few classical references are included, but for the part the references are to recent work. This rather haphazard selection of references has led, the writer finds in retrospect, to his giving prominence to his own work, and to some extent to that of his frequently failing out of all proportion to their importance, which he hopes will be forgiven. Such references as are given the writer believes are accurate. He mentions the more important work of others, he has to thank Mr Sur, librarian of the Calcutta School of Tropical Medicine.

## ILLUSTRATIONS

The majority of the figures and illustrations are original. When they have been borrowed from the books or papers of other writers the source is given. Permission to use these illustrations is gratefully acknowledged. The one or two exceptions to this rule are charts that have been taken from the museum of the Calcutta School of Tropical Medicine. It has not been possible to trace their source. The original drawings of the coloured plates were made by Mr H Roy, the artist at the Calcutta School, Mr Roy, Mr Mulhek (the assistant artist at the Calcutta School), Mrs Lawrence, and Miss Vera Morel the two latter of New Orleans drew the 'cycles' from the writer's very crude sketches. The assistance given by these artists is gratefully acknowledged. The assistance given by the 47th British General Hospital, for the loan of the skiagrams shown in Plates XIII and XIV and for the temperature charts from which Fig 135 was copied.

## ACKNOWLEDGMENTS

The writer's sincerest thanks are due to Lieut-Colonel Seward, Officer in charge, Medical Division, 47th British General Hospital, for reading through all the proofs of the earlier chapters, for pointing out many mistakes that had been overlooked and for making several valuable suggestions that have now been adopted, to Dr R N Chaudhuri for material help in several chapters and assistance with the proof reading, to Dr Harry Henkys for his useful note on bejel, to Dr Sundara Rao for his collaboration in the chapter on guinea-worm and for his assistance with the chapter on filariasis, especially for the photographs illustrating that chapter. Dr S K Ganguli for his collaboration in the chapter on snakes and ke-bite, and above all to Dr John Lowe not only for his contribution to the first part of the book and making many constructive criticisms, valuable assistance has been given by many of the writer's colleagues in Calcutta and at Tulane. His thanks are especially due to Dr Grace Smith, Associate Professor of Medicine, Tulane Medical School, for the first part of this book up to and including the chapter on leprosy was published in India in 1943. The completed book is now published in the United States. It has been possible to make a certain number of corrections and alterations in the previously published part of the book to conform with various reasons these have had to be strictly limited.

constructive criticism in the chapters on diet and dietetic diseases to Dr F H Wilson Associate Professor of Parasitology for reading the typescript of most of the later chapters especially those on helminthic infections and for pointing out many mistakes and inaccuracies to his friend Dr J Walker Associate Professor of Tropical Medicine for his caustic but usually helpful criticism especially in the chapters on malaria sleeping sickness and yaws to Miss A M Lyman for her careful reading of the typescript and to his secretary Mrs Virginia Gill for her accurate typing

The section of helminthic diseases was written in the helminthological atmosphere of the Department of Tropical Medicine of the Tulane Medical School where the writer has had the exceptional opportunity of supplementing his previous knowledge and personal experience of this subject by attending the excellent lectures and demonstrations of Dr E C Faust Dr J S D'Antoni and other members of the staff of the department He must however assume full personal responsibility for his interpretation of this teaching

The writer's special thanks are due to Brigadier G Covell CIE I M S Director of the Malaria Institute of India and to Dr R Kirk of the Sudan Medical Service for going through the final drafts of the malaria and sleeping sickness sections respectively for pointing out errors of fact and for making constructive suggestions While it was possible to make corrections and to take advantage of the suggestions it was not possible to send the proofs to these officers for final approval and the writer must assume full responsibility for the correct interpretation of their suggestions

For reading the page proofs of this edition I am very greatly indebted to Miss Joan McAllister and Dr David Weinman who kindly volunteered to undertake this task when I had to leave for Europe on very short notice

I am extremely grateful to The Macmillan Company who undertook the publication of this book during very difficult times and especially to Miss Marie Ranzini on whom a grave responsibility devolved while this edition was in process of manufacture

# INTRODUCTION

## THE EMPHASIS IN TROPICAL MEDICINE

Soon after Japan entered the war a number of army medical officers arrived in India from Great Britain and the United States and in order to initiate them into medical practice in the tropics classes were organized. It fell to the writer to conduct some of these classes. By way of introduction to his lectures he attempted to analyse the difference between medical practice in temperate climates (for which most of these men had received

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it would only be a matter of extending one's reading to include the rarer tropical diseases that are usually omitted from the more concise textbooks of medicine. He believes that the main difference lies rather in the special emphasis given to certain aspects of those diseases that are looked upon as

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presented rather than in the order of their importance.

**History**—Tropical medicine is a young, rather self-conscious branch of medical science much of its history has happened within the lifetime of the older of the present day writers and even though these writers may themselves have played little part in the historical events they often knew the principal actors personally. But this emphasis on history is more than

history of a disease and of the dis  
background for the proper appra  
which must never be looked upon

as final however complete it may appear to be.

**Epidemiology**—The diseases of Aberdeen are much the same as those of London or even of New York, Berlin or Vienna and although respiratory diseases may be more common in the winter and certain infectious diseases at other seasons there is no sharp segregation to any one time of year of the bulk of the diseases with which the practitioner in temperate

or each disease so that one knows how where and when to expect to encounter the disease and does not lightly diagnose kala azar in central Africa sleeping sickness in India plague in the Punjab in July or sand fever anywhere in the northern hemisphere in January. Other environmental factors also assume a far greater importance in tropical than in

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**Ætiology and prevention**—The bulk of the disease that one encounters in temperate climates are degenerative or chronic inflammatory diseases the prevention of which is outside the scope or even the thoughts of



the average practitioner, so that he has no further worry on this score, and, even when he does encounter an infectious disease, whether it be measles, influenza, or just a common cold, there is seldom much mystery about the mode of infection, which is usually by direct contact and/or droplet infection. He has only the household, or, in the case of an institution, the other inmates to consider, and, after that, the most he need do will be to notify the local medical officer of health. On the other hand, nearly all tropical diseases are of an infective nature and eminently preventable, so that the practitioner's thoughts should be for the community as much as for the patient. He must have a thorough knowledge of the etiologies of the

vector, an intermediate host, and/or an animal reservoir of infection. In fact with few exceptions, notably diseases due to the direct effects of a tropical climate, nutritional diseases, and the intestinal fluxes, the vast majority of tropical diseases are transmitted to man through the agency of an animal and/or an insect.

This is the type of problem that the practitioner in the tropics may have to face. Is it Weil's disease? If so, he will think, it would be interesting to know how in this case the infection was acquired, and whether there was an occupational association, but he should know that in the

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disease has not appeared in the locality before then he must give his full attention to averting a major disaster. After putting the patient under a

immediate thought. So perhaps most of all, the practitioner in the tropics must have a thorough knowledge of the etiology of all the diseases he is likely to encounter.

The writer has always felt that the tropics provides a field in which the physician and the public health worker can meet most easily and naturally. The physician is so often compelled to think in terms of prevention and the health officer has so often to invoke the aid of the physician to organize specific treatment campaigns as a means of limiting reservoirs of infection whereas they are nearly always mutually dependent on one another for accurate diagnosis.

**Signs and symptoms versus laboratory findings**—The populations with which one has to deal in temperate countries are usually relatively

When the Cumberland miner gets much the same course as it would in a London banker, and it is possible to give a clinical description that will cover both cases. It is not so with the vast majority of tropical infections. A patient may react to malaria infection in a hundred different ways, but the one common factor is the

presence of parasites in the peripheral blood. Further, the answers given by the illiterate patient, even if the language and dialect difficulty can be overcome, are often misleading, so that one is compelled to lay less emphasis on history and subjective signs and symptoms and more on laboratory findings

as important and necessary to carry out routine laboratory examinations of, at least, the stools, the urine, and the blood, as it is in any climate to make a thorough physical examination and to examine the patient's chest even when most of the symptoms point to the abdomen

On the other hand, laboratory findings are not allowed to outweigh clinical examination or to outweigh common sense. It is uncommon to find

*Entamoeba histolytica* cysts in the stools of a patient in whom kala-azar is present. Although each finding might be significant, there may be, in the particular case, no connection between these infections, and although in most instances one would attempt to free the patient from his hookworm and amœbic infections during his convalescence after treatment for kala-azar, return to normal health may be possible without the eradication of either of these infections. Nor does the discovery of all four of these infections exclude the possibility that the patient has some other disorder, such as a chest full of fluid, that demands immediate relief

Laboratory findings may be as misleading in some cases as they are useful and even essential in others, and, although the writer is in favour of routine laboratory examinations whenever it is possible to carry these out, it is very necessary that the findings should be given their proper perspective, viewed in conjunction with the whole clinical picture, and interpreted intelligently. The writer's early experience of tropical medicine was all in the laboratory. Even in those days he saw the danger of the complete laboratory domination of tropical practice, and he has fought very hard against this tendency ever since. He hopes that in this book, whilst emphasizing the great importance of the laboratory, he has succeeded in keeping it in its proper place

**Specific treatment**—Finally, in the matter of treatment, tropical medicine undoubtedly stole a march on the mother science. We had specifics for malaria, kala-azar, sleeping sickness, and certain helminth infections, not to mention the tropical spirochætal infections, when 'temperate' medicine could claim only salvarsan, unless one includes antivenine and diphtheria antitoxin one for each side. The vitamins, penicillin, the sulphonamides, and other new therapeutic substances have gone some way to even up matters but, case for case, specific treatment is far more important in tropical than in temperate medicine. Moreover, in tropical practice, conditions are often such that specific treatment is the only treatment that can be considered, and it is therefore given special emphasis. It should, however, be appreciated that general and symptomatic treatment may be almost if not quite, as important as specific treatment. If the writer on tropical medicine appears to neglect this aspect, it is because he assumes that the reader already has a sound knowledge of the general principles of medicine and expects that he will apply them. It is not because he wishes to diminish its importance



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THE  
PRINCIPLES AND PRACTICE  
OF  
TROPICAL MEDICINE



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## GENERAL CONSIDERATIONS

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The Genesis of Tropical Medicine—Present day scientific medicine was born and nourished through all its earliest stages in temperate western countries. When the people from the western civilizations invaded the East in a military or a commercial sense or simply as scientific or dilettante travellers they found that the medicine practised in many of these countries was the crudest form of traditional folk lore though in others, such as India and China there were established systems of medicine which intrigued these western invaders and from which the doctors amongst them gathered some useful recruits to the pharmacopœias of their own countries.

However, early in the nineteenth century the superiority of scientific medicine over  
victors but  
more practised  
from the West  
support them in the style in which quite justifiably they demanded to  
compensate them for the conditions under which they had to live, medical  
schools and colleges therefore were founded in the tropical countries to train  
the natives of these countries in methods of scientific medicine

About the middle of the last century, it began to dawn on the still conservative mind of the practitioner of scientific medicine in the tropics that, whilst the medicine that he had been taught was very much better than indigenous medicine, as it was then practised, he was frequently encountering syndromes to which there was no reference, or only very misleading references, in his textbooks. Amongst those who had the gift of being able to think ahead of their time and the energy to stir up others to take action with them, Patrick Manson stood out. Many of his predecessors and contemporaries played their several parts, and books on the diseases of various tropical countries were written, but it was Manson who gave this study of tropical diseases a definite form, a new branch of medical science came into being, and rightly Manson is looked upon as the father of tropical medicine. Through his energies the London School of Tropical Medicine was founded and for many years his book stood alone as the textbook on tropical diseases.

Nothing succeeds like success, and the early successes in the field of tropical medicine, which may be typified by Ross's work on malaria, stimulated this new branch of medical science, and other schools of tropical medicine were founded in Europe and North America.

From one point of view this awakening of interest in the study of tropical diseases had come too late, for already in certain tropical countries India in particular, in the medical schools and colleges to the founding of which reference was made above, western traditions of scientific medicine were firmly established. The men who had never been in a tropical conditions and the diseases that the course of study were faithful

practice. If he wished to gain special knowledge of how to treat these diseases, he had to go to London, Hamburg, or Baltimore.

this power was not vested in any central authority. It was Leonard Rogers who already had a world-wide reputation for his many researches in tropical medicine, who saw a way out of this impasse and, with the encouragement and a considerable amount of financial help from the commercial communities and large industries won over the official opposition and founded the Calcutta School of Tropical Medicine, for post-graduate instruction and research in tropical diseases. He hoped that in time the teaching in this school would have a leavening effect on medical education throughout India, and possibly in other tropical countries, not only in the final years of practical work but in due course in the physiological laboratories and possibly even in the dissecting rooms, and that when it had done its work and outlived its usefulness in this direction this school would remain as a centre of research and higher post graduate studies.

This is the writer's explanation of the anomaly of a post-graduate school in a tropical country where instruction is given to the local practitioners in subjects which should have been those most emphasized in their qualifying medical course

Defining the Scope of tropical medicine from the body corner and one hopes only a temporary separate it is and very corner it is possible to define its scope? It is certainly difficult. The problem

hesitates to give information that may be misleading but this state of affairs is changing. The next question is, how far should one go into the subject of tropical hygiene? This brings one to a wider question of medical policy, namely, the past tendency to separate the present hesitancy, and the future decision (we foretell) to link much more closely prevention and relief in medical education and practice. In his teaching of tropical medicine, the writer has solved this problem by laying special emphasis on the preventive aspects of specific diseases whilst leaving the subject of

for many diseases that are always looked upon as tropical diseases malaria, cholera dysentery, also occur in the temperate zone. So we must fall back on an elastic definition and say that under this heading should be included diseases that occur only in tropical and sub tropical countries, and also diseases that are either more prevalent or else exhibit special features in these countries

The Changing Picture—The position is not however static. Many diseases that were at one time world wide in their distribution are now confined almost entirely to tropical countries of these perhaps the best example is leprosy. Leprosy was a cosmopolitan disease common enough in England a few hundred years ago as is evidenced by the leper windows that still exist in many old churches but it has now disappeared almost completely from most western countries. Malaria has been banished from England and many other European countries and yellow fever from the east coast ports of the United States of America to become a disease with an essentially tropical distribution. Cholera and plague have probably

it seems possible that tuberculosis is now following the same way as leprosy. The 'white man's plague' has certainly changed its colour preference in America and has shown a steady decrease for nearly a hundred years in Great Britain, but it is rapidly increasing in many tropical countries, just as is cerebro-spinal fever another respiratory transmitted disease, in the crowded bazars of the east

**Diseases Uncommon in the Tropics**—There are diseases that are less common in tropical countries, *e.g.* rickets, most streptococcal infections, erysipelas scarlet fever, and carditis included in this category but is a sterile controversy regarding carditis in the true tropics has to time. The champions of the former view made their point many years ago, but are tending to push too far their claims for the frequency of the occurrence of rheumatic carditis, relatively and, almost certainly, actually, it is a far rarer condition in tropical than in most temperate countries.

Then, there are diseases that are supposed to be less common in the tropics, these include cancer, but it is very doubtful if this is really uncommon. Statistics are vitiated by the infrequency of post-mortem examinations, by poorer diagnosis and poorer facilities for treating the patients when a diagnosis is made, by a much lower expectation of life so that far fewer people reach the cancer age, and by the fact that the numerous other diseases that occur distract attention from cancer as a public-health problem, except in a few instances where its cause is patent, *e.g.* kangri-burn cancer of Kashmir. Enteric was another example, sixty or seventy years ago, there were many discussions in the medical journals as to why enteric occurred amongst British soldiers in India but never amongst the indigenous inhabitants, until bacteriology came along and taught us to recognize as enteric the slightly modified disease that is very common amongst Indians.

#### ENVIRONMENT AND THE DISTRIBUTION OF DISEASE

There are of course many cases that are inexplicable in our present knowledge of the exact aetiology of these diseases but have been collected over a period of many years, some of the factors that determine the distribution of diseases in tropical and in non-tropical climates, these factors can be classed as (a) climatic, (b) telluric, and (c) human.

**A. Climatic factors**—Climate is brought about by a combination of solar and terrestrial influences, though it is with the sum-effects of these influences that we are concerned, they must be considered first under a number of different headings—

(i) **Temperature**—This cannot be expressed as just hot or cold for hot climates exhibit wide variations in their temperatures and these temperatures cannot be given simple numerical expression there are climates that are hot throughout the year and others that have a very hot and a very cold season, some countries have a temperature that shows little variation during the twenty-four hours of the day, others one that whilst it is extremely high during the day drops very considerably at night and yet others that exhibit both these features but at different times of year. To convey a proper idea of the temperature of a locality, a full range of 'normal' data for the whole year should be given, but if it has to be expressed very concisely the best figures to give are the mean of daily means and the mean diurnal ranges for the hottest and for the coldest months of the year.

(ii) **Humidity**—This is expressed as—

- (a) absolute humidity in grams of moisture per cubic foot
- (b) relative humidity, indicating the percentage degree of saturation, 100 per cent being complete saturation at the existing temperature
- or (c) saturation deficiency, which indicates the drying power of the air expressed as the difference between the vapour tension at dew point and the actual vapour tension at the time in millibars

In one country there are wide differences in the humidities in different localities, from season to season and at different times of the day, the early morning

humidity, which is the one so often given, is always high and gives a very poor indication of the humidity of a place or a season

(iii) Air movements and prevailing winds—This is recorded in miles per hour or feet per second two miles an hour being roughly 3 feet per second. In the matter of wind prevalence, an important factor is usually whether the prevailing wind is from the land or the sea, but there are many other considerations too numerous to indicate here

(iv) Sunshine—This is recorded as the number of hours of sunshine during the day. This important factor appears to receive more attention in weather reports in temperate and cold climates

(v) Barometric pressure—Whilst this is subject to considerable irregular fluctuation localities of the same altitude above sea level do not show constant variations that would be likely to affect disease distribution. However the

has an effect on physiology and  
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ear it is expressed in inches per

tant factor in the make up of a  
climate both in temperate and tropical zones. Though storminess in temperate zones is associated with respiratory disease and rheumatism on the whole the balance is in favour of the stormy climates and Huntington (1924) goes as far as to say that it is the northward shift in the storm belt that has caused the northward and westward shift in the centres of civilization a view not in keeping with that expressed by the writer (*vide infra*)

A factor associated with this is atmospheric ionization and some medical climatologists attribute much in the balance of health and disease to this. Our knowledge on this subject is at present too vague to allow any helpful discussion on this factor

**B Telluric factors**—These can be considered under two headings—

(i) Natural—The physical and chemical nature of the soil the sub-soil water level vegetation etc and the physiographical configuration of the terrain

(ii) Artificial—Irrigation and drainage afforestation and deforestation the building of cities (that shut out air and hold the heat) etc

**C Human factors**—These include the density of the population and the degree of urbanization, and industrialization to which they have been subjected

populations

Variations in these climatic telluric and human factors from place to place will determine the geographical distribution of disease, from year to year their epidemic occurrence and from season to season their seasonal incidence. Nearly all these factors are interdependent and, as they never act singly, it is seldom possible to judge the effect of one alone—e.g. the effect of the humidity and the atmospheric conditions are not independent. Taking account of the humidity, the purity of the air, and the various factors in the Punjab is holera

## CLIMATE AND DISEASE

How do climatic conditions prevalent in the tropics bring about tropical diseases? They act directly and indirectly

**A Direct effects of climate**—The compensatory mechanisms of the human organisms are so elaborate that the direct effects appear to be remarkably few, this is shown by the fact that the physiology of man living in the tropics is basically the same as that of man living in the arctic zones. There are certain immediate reactions to change to tropical climatic conditions that are rapidly adjusted or compensated. These can be imitated in the laboratory or ward, have in the past been studied frequently, by physiologists, and are now, since the introduction of hyperthermal methods of treatment, receiving the attention of clinicians. At the other end of the scale, time measured in centuries produces certain fundamental changes in the human frame which are of interest to ethnologists, but here one is uncertain whether the effects of climate producing these have not also been indirect, through diet and other environmental factors. Between these extremes there are the results of the subjection for months, for years, and for generations to tropical climates, and it is these that are of special interest to the physician. Beyond the observation and explanation of certain obvious differences between the inhabitants of the temperate and tropical countries, such as that of colour, the subject of tropical physiology has been neglected, and until this gap in our knowledge is better filled, we shall find our study of the pathological effects handicapped.

**The sun's rays**—Fundamentally the cause of the difference between tropical conditions and those of the temperate zones is the fact that the rays of the sun are more direct and therefore, other things being equal, produce their effects with greater intensity in the tropics, it will thus be appropriate first to consider what are the direct effects of these sun's rays on the human body. These effects can be classified according to the different rays which strike the earth, thus —

Spectral classification	Effects	Angstrom units	
1 Ultra violet	} Biochemical rays	1 000 -	3 900
2 Violet		3 900 -	4 300
3 Blue		4 300 -	5 000
4 Green	} Luminous rays	5 000 -	5 600
5 Yellow		5 600 -	5 900
6 Orange		5 900 -	6 200
7 Red	} Heat rays	6 200 -	7 700
8 Infra red		7 700 -	120 000

We have very little data regarding the relative power of the ultra-violet rays in tropical and non-tropical countries, but usually there is less interference with these rays in their passage to the earth's surface in the former and their effect is therefore greater. The ultra-violet rays have a low power of penetrating skin and subcutaneous layers of the skin, children in tropical countries are unduly protected from exposure to the sun.

On the skin, the most noticeable effect of the ultra-violet rays is an erythema which comes on two hours after the exposure and reaches its maximum in about six hours, this will vary in its severity and in extreme cases will lead to severe blistering. Repeated irritation by exposure will

lead to chronic changes in the skin (*vide infra*) The wave length produces this erythema is from 2800 to 3100 Å. The natural pigmentation in the skin of the indigenous inhabitants of the tropics acts as a protection against this effect of the ultra violet and even amongst the white races the brunette is usually less so than the blonde. The pigmentation that follows repeated exposure to the sunlight is brought about by rays of slightly longer wave length including the visible rays.

The unhealthy pallor of the skin that is often seen in the European sojourner in the tropics is due to the excessive zeal with which he—often she—has protected himself from the beneficial sun's rays coming with unhealthy living and in many instances disease.

The luminous rays again are usually stronger in the tropics than powers of penetration are greater than those of the rays of shorter wavelength and they probably have a stimulating effect on the blood and tissues as well as a detrimental effect on parasitic micro organisms. Our knowledge on this subject is more speculative than precise. The action on the retina is more certain in excess they cause headaches, reduction in visual acuity, a decrease of adaptability to comparative darkness which may become pathological in special circumstances (night blindness), and other pathological changes in the retina.

However probably the most important are the heat rays both the physiological and the pathological effects of the heat rays on the body temperature have been studied in rather more detail than have the physiological effects of the other climatic factors. Before considering the effect of heat rays, one must review the physiology of heat balance.

**Heat balance**—Heat is produced by the cellular combustion of foodstuffs. Only some 20 to 25 per cent of this heat is converted into energy and the balance has to be dissipated. If this heat is not dissipated the body temperature which in man and other warm blooded animals is normally maintained at a constant level will rise and the physiological processes of the body will be interfered with. To maintain this constant level there must be a balance between the heat that is produced by the metabolic processes of the body and the heat that is lost to the surroundings. Under tropical conditions the rate of this heat loss is reduced and there are times when the process of balancing the heat account is complicated by the fact that certain items that are normally on the debit side are now transferred to the credit side of the account, i.e. when the atmospheric temperature is higher than that of the body and heat is actually absorbed from the environment.

**Heat production**—In an average man (whose weight is usually placed at 70 kilogrammes or 154 lbs, though the figure is too high for the individuals of many races e.g. southern Indian) average weight about 20 lbs) normal body functions produce about 100 calories an hour at rest work accelerates heat production and a soldier marching with a pack weighing 6½ lbs will produce 8 calories per minute.

**Heat loss**—Heat is lost by radiation, conduction, convection and evaporation. For practical purposes the means of heat loss can be considered as 'sensible' loss which includes radiation and conduction to surrounding cooler objects and convection that is loss to the air in contact with the body surface—this air absorbs heat, moves away and is replaced by fresh air when the process is repeated—and latent loss which is achieved by saturated air absorbing moisture from the body surface from the



Finally, beyond this 'discomfort zone' conditions are encountered under which man cannot survive for any length of time without his temperature rising, the hyperpyrexia and shock that may result from subjection to such conditions must be considered under the heading of 'diseases due directly to climatic conditions' (*vide infra*)

**Other Physiological Effects**—Some of the effects of tropical climatic conditions on other body functions and systems can be briefly reviewed

A change to a tropical climate is accompanied by an increase in blood volume which is apparently a dilution for corresponding relative reduction of the solid elements are concerned, with little evidence that the increased volume is to heat equivalent to that frequently encountered in even moderate tropical climates will lead to a temporary increase in pulse rate (see figure 2), but the normal pulse rate of the inhabitant and of the sojourner in the tropics (this term is used in reference to those who normally live in a temperate climate but are temporarily living in—not just travelling through—a tropical country) is about 75

The blood pressure of the sojourner is apparently not materially changed by residence in the tropics, though possibly low blood pressures are more frequently encountered than in temperate climates. On the other hand that of the indigenous inhabitant is distinctly below the European and American standards (Cadbury, 1922, Kean 1941)

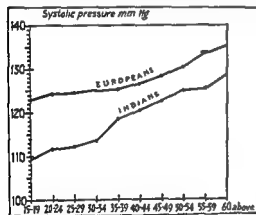


Figure 3 Blood pressure of different age groups

than the European standards at

southern and eastern Indians (from Madras and Bengal) Meat eaters showed pressures 1 to 2 mm higher than the pure vegetarians

The respiration rate after acclimatization is apparently slightly decreased but the volume of each breath is increased. There is—judged on balance of conflicting evidence—a slight decrease in the normal basal metabolic rate, and this corresponds with the lower calorie requirement of the tropical resident

Exposure to high temperatures is said to depress haemopoietic function. The 'thin' standards closer to the (ably higher) higher than even the American standards (Napier and Das Gupta, 1942). The higher

hæmoglobin normals at high altitudes is recognized as a compensatory mechanism and it is probable that a greater oxygen carrying power of the blood is necessary to counter balance the lower oxygen tension in the hot air of the tropics

Moderate heat will cause a rise in the leucocyte count (see figure 2) but this is apparently not maintained for the average leucocyte count in tropical residents is certainly not higher than in residents in temperate zones. There is however evidence that the stimulation of the leucopoietic tissue is maintained for there is a persistent shift to the left in the Arneth count indicating a more rapid turnover of polymorphonuclear leucocytes which in many cases is unassociated with infections. There is also a persistently higher eosinophil count but it is impossible to exclude causes other than the climatic conditions for this

cooler climates and consequently fail to rise to the occasion in diseased conditions. There is some effect on the sex glands for on the whole the inhabitants of the tropics tend to reach sexual maturity earlier and they are certainly liable to an earlier decline. Mills (1941) takes an opposite view and quotes figures in support in which he shows that Panamanian

The sex urge of the sojourner is popularly supposed to be stimulated on arrival in a tropical country but it is possible that this is a false impression created by the reduced opportunities for legitimate and the increased opportunities for illicit relief

The digestive functions—Independently of food requirements that are slightly but distinctly lower especially with reference to fat and protein—writer and his co workers the statement frequently topics in our experience in British and American condition of the gastro

intestinal tract is commoner amongst sojourners especially women than amongst the same persons living in cool climates but there is little evidence of this in the local inhabitants and it is difficult to exclude bowel infections as the cause. The hyperæmia of the skin induced by a hot climate may lead to an ill distribution of blood and a relative ischæmia of the digestive organs with resultant hypofunction

rate per se are hard factors. The nervous life of sojourners is themselves to local evidence of this in

the indigenous population or in the more moderate and more adaptable sojourner. Similarly there is little evidence that tropical neurasthenia is a direct climatic effect though here again the monotony of the tropical heat

fails to provide beneficial periodic stimulation. Failure of memory, which is referred to as West Coast memory, Bengal head etc., according to the locality, though it is common in all tropical countries, is probably more result of the environment and the circumstances than actual temperature and may be a manifestation of a mild form of neurasthenia, associated with inability to concentrate. On the other hand, neuralgias are certainly less evident in a hot than in a temperate climate.

There is no evidence that ultra-violet rays of the sun have any direct action on the brain or spinal cord, they do not in fact penetrate even the skin, and certainly not the skull. But the visible rays may have an effect on the retina causing a temporary and in certain cases a permanent reduction in visual acuity and also night-blindness (*vide supra et infra*) these changes may react constitutionally and produce headaches, vomiting, and other symptoms often wrongly attributed to the direct action of the ultra-violet rays on the brain and cord.

The evaporation mechanism of the inhabitant in the tropics is attuned to the local conditions, and their 'invisible' perspiration is much more effective in keeping down body temperature than the profuse and wasteful perspiration of the sojourner. This helps to explain the greater frequency of heat ill-effects in the latter (Lippmann, 1942).

The continuous hyperæmia and moistness of the skin in the tropics probably does not actually produce any pathological change, but it tends towards the blocking of the sweat glands, it allows certain infections to establish themselves more easily, and possibly it prevents others.

**Pathological changes**—When the compensatory mechanisms of the body fail or when the changes brought about by extreme environmental conditions have passed beyond the physiological limits the conditions produced must be classed as diseases (*vide infra*) caused by the direct effects of climate.

II Indirect effects of climate—Whilst the direct effects of tropical climates can be dismissed in 2<sup>nd</sup> order, the indirect effects form the subject matter for the rest of this book. The indirect effects of climate are determined by the nature of the local climate, the state of nutrition of the population, the deficiencies that prevail amongst them (b) of the bacterial, protozoal and helminthic parasites that are the causal organisms of disease, (c) of the insect life that transmits these causal organisms to man and/or (d) of the animals that carry or act as reservoirs of infection, or climate acts, (e) by favouring, or the reverse, the natural enemies of insect vectors and animal reservoirs of infection, and (f) by determining the balance of biological competition amongst insects, fish, birds and mammals.

f Theoretical—There is scarcely any limit to the indirectness of the ways in which climate may react on the distribution of a disease and the important climatic factor may appear at first sight to have as slender a connection with the particular disease as the crow with a crumpled horn had with the house that Jack built. For example the normal climate in a locality might favour a certain crop that was parasitized by an insect that was the main food supply of a bird that fed alternatively on another insect that was the transmitter of a human disease. A bad year (climatically) might lead to the failure of the crop which one would expect would lead to a dearth of the parasitizing caterpillar so that the bird would have to turn its attention to the disease transmitting insect with the resulting fall in incidence of the human disease.

The effects of climate may thus be not only indirect but very complex and difficult to explain. If to follow the hypothetical case given above one wished to explain the decrease of the disease on the climatic factor it would not be safe to assume any single step in the effects and counter effects it would be

essential to ascertain whether unfavourable conditions to the plant did in fact cause a decrease in the caterpillar population, or whether, as often happens interference in the nutrition of a plant led to an increase in parasitization, whether the birds actually were induced by shortage of their primary food to take their quota of the disease-carrying ble epidemiological effects of certain

climatic factors are dangerous and as often as not have to be reversed when actual investigations are carried out

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# MEASURES FOR MITIGATING THE EFFECTS OF TROPICAL CLIMATE

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**Introduction** —The early civilizations were all in warm countries, here primitive man found food plentiful and life comparatively easy, so he had

cooler climates, and the centres of civilization were in the north. Now we are learning how to control our environment in hot climates also, and it seems possible that this drift may be stopped or even reversed

The history of civilization has been described as the story of man's

Here we are concerned especially with a tropical environment and we have discussed above the ways this may influence the health of man. The effects may be direct or indirect. The major portion of this book is devoted to the indirect effects, to the means by which we can counteract these before they produce diseases, and, when we fail in this, treat the diseases that are produced. In the previous chapter, the direct effects of the tropical environment were discussed, the present one will be devoted to the mitigation of the direct, and in a general way the indirect, effects of the tropical environment by the adaptation of man to this environment and of this environment to man.

The subject will necessarily be considered more from the point of view of the foreigner, as the local inhabitants will already have achieved a degree of adaptation, especially to the more obvious direct effects. Their practices should be studied but never adopted without critical examination and they are quite frequently unsound, further, they are seldom directly

the amenities that recent generations have superimposed

dependent that has been written on the  
dependent on analogy and guess-work,  
he guess-work will have to continue to  
usually more susceptible to temperature  
changes, are by a process of natural selection capable of acclimatizing  
themselves slowly to changed conditions, but the process takes many  
generations in the more complex and more adaptable human individual,  
the same process will take many more generations, so that racial  
acclimatization is measured in millenia

Individual acclimatization is largely a matter of the adaptation of

his general behaviour are very similar to the indigenous inhabitant

What are the usual reactions of the European or North American who spends the best part of his adult life in a tropical country, to the heat?

The first year he usually finds particularly trying, but he learns how to adapt his habits, and settles down, taking the climate as he finds it, though naturally grumbling in the hottest weather, for the next 15 to 20 years, after this he finds each hot weather more and more trying and the thought of retirement dominates his mind, unless he can get away early in summer. There are of course other factors, such as disease and age, but at least the effects of acclimatization are not very apparent.

Amongst British troops under arms to some extent due to racial acclimatization, but even here



It is of course essential that all the vitamins should be well represented in the diet. The most common deficiencies are associated with vitamins B complex, C and A in that order, and iron. In an ordinary mixed European diet and in the ordinary diet of the well-to-do Indian, none of these is lacking. In the tropics, however, the deficiency of vitamin A is often pronounced. In the tropics, therefore, it is medically recommended to take a concentrated source of vitamin A.

Constipation is a common complaint amongst sojourners in the tropics, even more so than it is in their own temperate climates, it is enhanced by the dehydration that is likely to occur unless plenty of fluid is taken, and by the tendency of the jaded appetite.

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of a grape fruit that has been kept cut side downwards overnight in an electric refrigerator. Similarly, twice cooked food whilst best avoided, as each cooking lowers its vitamin content and usually its digestibility, need not be looked upon as a positive danger in these days of electric

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water and the washing of salads and fruit so that it can be checked any day, even if he does not check it every day.

The kitchen or cook house, far too often a ramshackle outhouse, is the one room in the establishment over which the greatest sanitary care should



be exercised (*vide infra*). It is not always possible to have a white-tiled kitchen, but a high degree of cleanliness can be attained without this refinement. Above all it should be inspected regularly, and also at odd

complaining at the same time that they find it difficult to fill their day. When such a housekeeper is adjusted to new conditions, but this is more often the pose of those who never saw a domestic servant in the homes from which they originated.

Another matter closely associated with food is the servants' dusters, tea-cloths, glass-cloths, dish-cloths, etc. Native servants will, if possible, convert anything that is given to them into an all-purpose cloth, which in addition to the above functions will be used for mopping their brows, wiping their noses, straining the soup, and finally, when cold drinks are demanded, for breaking ice in. The potential dangers of such a practice are more

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Much preventable ill-health amongst the sojourner is directly attributable to the 'studied' indolence of their women, and the writer regrets that those of British origin are apparently the worst offenders.

### *Beverages and Alcohol*

The question of what to drink, which may be an unimportant one in temperate climates, looms very large in a tropical country, because, when evaporation plays such an important part in maintaining a normal body temperature, the physiological requirements of water are much greater. Not only should one's thirst, which is the outward and visible sign of water depletion, be satisfied, but a definite amount of fluid should be taken as a routine, for example, it is a good plan to drink a glass of water on rising in the morning. In hot dry climates, when moisture depletion is considerable, it should be remembered that a considerable amount of salt is also lost in perspiration and that this is not replaced by water, so that it is a good practice to make a habit of taking a tablet of at least 10 grains of sodium chloride with each glass of water.

The greatest obstacle to teetotalism in the tropics is the absence of a 'soft' drink that is really acceptable to the male palate. The 'windy insufficiency' of these is more than an excuse, it is very frequently the reason, for the resort to beer or whiskey and soda to quench an honestly earned thirst. It is of course unnecessary to drink gaseous lemonades or to add soda to sweet drinks, but even drunk 'still' they are very nauseating to many people. There is of course nothing more refreshing than to get from a bottle kept in the refrigerator, if the taste of the water

There is also very much to be said for, and taken after the day's work its to put off the hour when the whiskey early made can be a very good drink, lime is more popular. The neat juice

of citrous fruits such as oranges, grape fruit, lemons, or limes, which are often abundant and cheap probably make the best long drinks and are an important source of vitamin C, and tomato juice has been the salvation of many, particularly women, who do not like to refuse to drink, but dislike alcoholic cocktails.

About alcohol, it is not possible to lay down any hard-and-fast rule. The pernicious fable that it is necessary to take alcohol every night 'to ward off fever' is happily dying, but alcohol, taken in strict moderation, in the evening to ward off depression that often follows the sinking of the sun is a valuable psychological stimulant. For this and other reasons the writer would hesitate to recommend teetotalism to the white sojourner who with his parents before him has probably been used to taking a moderate amount of alcohol, except in the case of one who has already shown instability in this matter, or who has a family history of dipsomania.

### working capacity

Regarding the safety of drinks taken outside one's own house, it should be remembered that converting water into soda-water does not sterilize it, nor does the addition of alcohol, in the strength in which it is drunk in the ordinary whiskey and soda, make doubtful soda-water safe. Where a drink has to be taken in a strange place, the only safe drink is coconut water, and this is better drunk directly from the shell than from the very doubtfully clean glass that is often offered to one. It is also incidentally as refreshing a drink as any non-alcoholic drink that the writer knows.

Of the alcoholic drinks, whiskey with soda, or better still with water, is the best long drink, and gin and lime juice or bitters, not too 'short', the best cocktail. Mixed cocktails are not to be recommended. Light beer is quite a good drink, but does not suit everybody, and wines do not usually keep well in the tropics, but half a bottle of wine, red or white, with the evening meal, instead of spirits earlier in the evening, may be taken without detriment by those who prefer to drink with their meals.

### Work and Leave

Western sojourners in tropical countries have brought with them many of their own habits, and amongst these is a restless energy that expresses itself by observing much longer hours of work than the indigenous inhabitants in many countries were previously accustomed to, including working through the heat of the day. There is much to be said against this practice, and, except in large towns where workers live a considerable distance from their work and where therefore a mid-day interval would be of little use to them, it is wise to arrange the working hours in such a way as to take advantage of the comparative cool hours in early morning and evening. For instance, if the day is divided into three parts, the first part for rest, the second for work, and the third for rest, the day can be divided into three parts, the first part for rest, the second for work, and the third for rest. In the morning, six hours of work can be done before mid-day (that is, 2 to 3 hours before the peak is reached) and the rest of the day's work in the comparative cool of the evening.

Whilst a full day's work is certainly not to be discouraged, every rule or at least a different, rules allow the accumulation of one's service. This view of the framers, tired rather than a part of the individual breaks down and he does year spells are the home leave in most between leaves should be possible and senior possible, for the sake of work should be punctuated by short breaks of even as little as ten days, whenever this can be managed, and the doctor should take every opportunity to order it getting away for a no valid reason, thus making the necessary

arrangements

### Exercise, Rest, and General Habits

In the tropics, where the temperature is so high, the natives find that walking a little cycling or itself in reasonable measures a little more. At the other end of the scale, where the temperature is so low, one is very tired and needs a certain amount of rest and drink.

that the need for regular exercise requires to be more emphasized

with the latter exercise is frequently a fetish and is more often overdone than neglected. It is a common fallacy that the early morning exercise expiates the sins of the previous night. Though there are individual variations in the matter of exercise requirements, just as in everything else, it is very largely habit and/or gastronomic and alcoholic excesses that lead to the remark so often heard from the sojourner 'I must have my morning exercise, or I cannot get through my day's work'.

Another fallacy is that a man can be controlled by exercise alone. Figures worth effects of only two to five hours of strenuous required to dissipate

that, if he cut down his evening meal to two not only would he feel very so tired at the end of the day but his health is not the fault of the exercise. The majority of (prematurely), but the earlier

Exercise should be graded according to age—football, hockey, hard singles tennis, and squash rackets are for the young, cricket and mixed tennis can be continued into the forties, after which golf is the game of choice. Riding can be graded to suit all ages, and walking and swimming are always useful alternatives, the last-named being particularly valuable in special conditions such as pregnancy.

As important as exercise is rest. The traditional mid-day siesta is not observed by the majority of sojourners who have their livings to earn, and, except in very hot climates where there is a mid-day break in the daily routine, it has little to recommend it, though for children nearly always and for women in many circumstances, it is a good practice.

There is probably no single factor more important in the general maintenance of health than a good night's rest, and, as it is difficult to sleep after about 6.30 in the morning in most tropical countries, early retirement to bed is essential (see p. 30).

On the whole, smoking is probably more detrimental to health in the tropics than elsewhere. This may be because cigarettes and cheroots are the more common media than the less detrimental pipe. Idle and neurotic women are particularly liable to become 'chain smokers'. It is more frequently on account of gastric disturbances than the toxic action on the heart that one has to recommend abstinence from this practice. There are also the writer's experiences of a more non-smoking atmosphere in the tropics.

Finally, advice on personal habits can be summed up in the simple counsel—admittedly one of perfection—moderation in all things.

### *Clothing*

In the matter of clothing, it is probable that we can add little to time-honoured local practice, the very scanty clothing of the South Indian coolie and the light loose clothing, easily thrown off the shoulder, of Indians of the educated classes are eminently suited to the hot damp



Quiescent abdominal infections are sometimes stimulated into activity by local chilling which the cholera belt was designed to obviate, it is therefore advisable for those subject to attacks of diarrhoea to put their wraps round their abdomens, rather than over their shoulders, when cooling off after exercise

Long stockings that were at one time nearly always worn with shorts are now often replaced by very short socks that do not come above the ankle, or ordinary socks rolled to the ankle, these should be of cotton or silk *Women seldom wear stockings in these days*

'In the Malay States, they have hats like plates which the Britisher won't wear', sang the satirist, nevertheless, we have probably made some advance in the matter of suitable headgear and in most instances have improved on the local customs, though even in this there is a great deal of pseudo-scientific nonsense written and talked by the 'trade' The essential features of suitable headgear is that the brim should be wide enough—at least 5 inches—to shade the eyes and the back of the neck, be light in weight and colour, be held well away from the head, both at the brim and over the vault—air is an excellent insulator—and be well ventilated by generous openings to ensure free interchange of air These features are not incompatible with a headgear of reasonably æsthetic appearance from the point of view of male fashions, and a fantastic shape is no guarantee of a scientific conception

European women are recommended to adopt the 'severe' male style and not to attempt to disguise a pith foundation as a recent fashion model, the attempt is always a ludicrous failure

with a wide brim, is in most cases adequate from the point of view of interrupting the sun's rays, but neither is so well ventilated as the pith 'toper'

The protection of the eyes is more important than that of the head,

produce very severe headaches

Footwear again will depend on the circumstances It would be inadvisable to advocate canvas shoes for tramping through excreta-contaminated soil on tea estates, but for town wear they are far better than leather, in that they allow freer ventilation, 'co-respondent' shoes, made with white canvas in the place of buckskin, are smart enough for town wear and are an excellent prophylactic against 'foot-rot', i.e. tinea infection with septic complications (*vide infra*) 'Mosquito boots', with

high canvas tops, are useful for protection in the evenings in mosquito-ridden localities

### HOUSING AND SANITATION

Much can be done to mitigate the ill-effects of the tropical climate by suitable housing. The design of a building will naturally depend on economic considerations, the average sojourner and his requirements will of course vary with the climate and on other local considerations, on whether it is a hot dry climate or a hot damp climate, and whether in the latter case the rainfall is so high and the drainage of the soil so poor that it will be necessary to have the house raised off the ground, or, in extreme cases where flooding is common, built on high stilts, or conversely whether the damp rising from the ground into the walls of the house will be welcome as an aid to temperature reduction during the hottest time of the year, again whether the walls should be thick and the house built so that it can be hermetically sealed during the hottest parts of the day (as for dry climates), or whether it should be constructed so that the maximum fresh air will be available throughout the 24 hours, whether it should be built to withstand heavy rainfall or if this is so rare that no allowance need to be made for it, whether it is to be in a town or in the open country, whether it will be necessary to make the building mosquito-proof, or not, whether its rooms are to be artificially cooled, or whether cooling will have to depend on natural methods, and so on

It will be obvious that the subject of housing in the tropics is a very complicated one. It has seldom been studied scientifically, except as a purely local problem to meet immediate requirements and is still almost entirely in the hands of the amateur, and often not a very intelligent one at that.

When looking at an old house built a hundred or more years ago, in India for example, one often hears the sigh 'Ah, they knew how to build houses in those days.' They did in fact use common sense and build houses with very thick walls, with broad verandahs to act as shade, and the large inner rooms, like the verandahs, were open to the air, even if we wished to do so. The architect had to adapt himself to changed circumstances and if he has not been very successful he has the excuse that science has provided him with very few data. Since modern tropical institutes are tending to be founded, one hopes that the subject will attract the attention of that future writers on tropical climates will depend entirely on the few crumbs of scientific investigation, such as that of Crowden, the importance of which they have to exaggerate in order to disguise the poverty of the meal that they are giving to their readers.

**Present day trends**—The general tendency today is to build the walls of the houses less thick than formerly, primarily because of increased cost, but the thinner walls, if insulated with the low-heat transmission material, have certain definite advantages over the old type of building with very thick walls.

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\* Mr B Dyer, professor of sanitary engineering, All India Institute of Hygiene and Public Health, Calcutta, has kindly supplied some of the data given below.

In the old houses with walls 3 feet thick built of low-density brick and plastered inside with a difference of 10°F between the indoor and outdoor temperature there was a heat transmission of 126 BTU\* per hour. With a 12-inch wall of the same type of brick and 1 inch of insulating material such as Celotex and the same conditions as above, the heat transmission would be 160 BTU per hour but, with a wall 18 inches thick with 1 inch of insulation the heat transmission would be 130 BTU per hour. There are obvious advantages in thinner walls if the insulation is equally good, not the least of these is that they are dryer.

bricks are poorly burnt and the mortar is of lime and sand, with too great a proportion of sand

The best roofing from the point of view of heat deflection, is thatch, the thicker the better, but it has certain disadvantages, in that it makes an excellent harbourage for rats, birds, snakes, and insects of many kinds and it is easily fired and has to be repaired very frequently. Rats and birds can be kept out by suitable wire netting.

Pitched roofs are usually of tiles, a composition asbestos material, or galvanized iron, and flat roofs are of brick and concrete. The galvanized iron roof which is cheap and serviceable is not as hot as one would imagine, provided it is painted white and there is a false roof of Celotex, or some other efficient insulating material, to intercept the radiated heat. Celotex is also used in conjunction with concrete, but brick rubble on top of concrete is also very efficient.

A pitched one-inch tile roof with a plastered ceiling has a transmission	at of a two inch
	concrete roof is
	1 inch insulation is
	a transmission
	and with 1 inch
	concrete under
	337 BTU

A pitched roof should overhang the walls of the building by at least

rays of the sun

The roofing material that has been introduced by Crowden referred to above, consists of three layers, the important layer being the centre one, this consists of a quarter of an inch of thickness of some composition material, the actual nature of which is not important, covered on either side by a very thin layer of aluminium or aluminium foil. The nature of

swords into plough-shares and our aeroplane scrap into aluminium foil, it may find a wider application. The coefficient of transmission of this

\* BTU = British thermal units



roofing is in the neighbourhood of 0.23 BTU per hour per square foot for each degree of difference of temperature between the inside and outside temperatures

Floors should be of finished concrete, terrazza or one of the new materials which are so attractive and, having a smooth finish, take a high polish. All the corners, and the angles between the walls and the floor should be rounded to permit easy cleaning.

Ground floors should be at least 18 inches above the ground, and there should be sufficient grated openings on all sides to provide cross-ventilation for the space below the floor.

The ventilation space below the floor has the disadvantage of forming a harbourage for reptiles, rodents, and other animals, and it is a continual source of expense to keep the grating or wiring in a proper state of repair. For this reason a solid plinth is favoured in some places, this must be covered by good concrete to prevent the damp rising up into the house.

Ceilings should be extremely high in room or house. A ceiling of 12 ft. of the room is necessary for conditioning.

Windows should be of the casement type, and, if no shutters are provided, should swing outwards. It is a great mistake to have windows too small. They should be 2½ feet wide and 5 feet high, but, even more

Good wooden shutters with fixed slats are a great help in keeping down the temperature of the room, and can be used with the glass windows open or closed, according to whether the air is to be shut out or free ventilation encouraged.

Doors should be wide, outside doors should have lintels and also be placed to assist cross-ventilation.

Screening of doors and windows should be done in all malarious countries, whether other anti-malarial measures are adopted or not. The old belief that screening raises the temperature of the room considerably is not borne out by the observations made by many investigators, though it does diminish air circulation. In the Punjab, rented flats must be screened by the landlords, as are government bungalows. The wire-netting should not be coarser than 16 meshes to the inch in order to exclude mosquitoes (see also *Malaria*).

The verandahs should be at least 12 feet wide and of sufficient length to be comfortable, there is a great advantage, in a country bungalow where space is unimportant, in having a verandah all round the house to protect the room walls from the sun, but in a town where space is necessarily limited, when the verandah is to be occupied much during the day, it should face east or north.

The aspect of the house is an important point, but no hard-and-fast rule can be laid down. The full range of local seasonal conditions must be considered. In Calcutta, for example, the prevailing wind in the hot

weather is from the south, in the cool weather when the wind may be too cold it is usually from the north, and storms usually come from the north west so that, despite the disadvantage of the hot sun during the middle of the day, the south is the aspect of choice.

The rooms should be of good size, at least 15 feet square or its equivalent. For country bungalows much larger rooms are the rule and are to be recommended provided air conditioning is not to be installed, but, if it is, there is a great advantage in a small room, which will usually be sufficient for ordinary living rooms or bedrooms when properly arranged. For example, wardrobes and cupboards (almirahs) are unsightly and are favourite nesting places of mice etc. Built-in cupboards are more convenient and save space. The old claim that they are damp is not applicable to modern building construction and has been found to be untrue in many tropical countries.

The kitchen, or cook-house, should have a considerable amount of

The smell of cooking is no direct closed house, even when ants are made to do be very offensive—

in their quarters, this objection is largely removed.

**Bathroom and toilet**—It is usual in the houses of sojourners in hot countries to have at least one bathroom attached to each bedroom, and, as in the hottest weather two or three baths are often taken during the day, it is worth while having the bathroom as large as possible, and fitted with a fixed bath and hand basin and a sufficient number of convenient shelves. A shower and an electric fan are comfortable additions. The floors should be made of polished concrete, which should extend 5 feet at least up the walls, the rest of the walls and the ceiling being painted.

If the spaces under the basin and bath cannot be completely enclosed in concrete, or some other vermin proof material, it is better to have them altogether open as the space is always damp and therefore an ideal refuge for cockroaches, centipedes, rats, or even snakes.

It is usual to have a flush toilet pan or commode in the bathroom, it is a convenient arrangement where the ratio one bathroom per person can be maintained, but otherwise it has obvious objections.

When there is no connected water supply and drainage, a commode with an enamel ware pan is usually used in India, but this necessitates the continuous services of a 'sweeper' which may not always be possible. The larger type of bucket latrine with an automatic ash sprinkling arrangement,

or simply a box of ashes and a shovel, has very great advantages over the shallow enamel-ware pan where service is irregular, and is popular in many tropical countries

For garden use, the bore-hole latrine with a light superstructure that can be moved biennially is very satisfactory in most soils, and has the advantage of being cheap (For 'rural water supplies and sanitation' see other sections)

### ARTIFICIAL COOLING

In a dry climate, use should be made of the *khus-khus tatt*. This is a screen of loosely woven coconut fibre that is hung across a doorway or over a window opening, it is kept continually saturated with water by some automatic feeding device or by hand with the help of a garden hose. The dry air comes in contact with this damp screen and causes evaporation which absorbs the heat from inside the room. This arrangement can be made more efficient by the use of a suction fan to draw the air through the screen. It is a surprising fact that this does not tend to make the atmosphere of an occupied room moister than when it is just closed up in the ordinary way, but it makes it a number of degrees cooler.

Air-conditioning in offices and houses—Twenty-two years ago when the School of Tropical Medicine was opened in Calcutta, one of the largest cities in the tropics, our 'cool' room was one of our most popular exhibits. It was an extravagance that was only justified by the fact that a large freezing plant had to be maintained for storing and preserving sera, etc., and that the cool room was necessary for certain chemical and bacteriological experiments. Its existence was dependent on the foresight of Sir John Megaw, who seven years earlier, before the 1914 war, had seen the necessity for, and designed, this room, and it was appropriate that he, the first director of the School, should be the one to make the most use of it. Gloomy prophets foretold that the users would be victims of all the worst ills that, in a tropical country, chilling is popularly supposed to generate, quite forgetting that in temperate and cold countries people are subjected to many-fold greater temperature changes every time they enter or leave their heated houses or rooms. These ill-forebodings did not materialize, and today our prize exhibit of 1920 is of little interest to visitors of 1942, many of whom have similar installations in their offices and houses, and we are compelled to stress the historical interest as an excuse for showing it at all.

and, had  
col, quiet  
lvantages  
and other  
flying insects with a high bulbous paint air entrance, as a rule the light  
can be shut out far more effectively than when one has to rely on open  
windows and doors for ventilation

The principle of the cool room at the School is a very simple one, air is driven over frozen pipes and conveyed by an insulated shaft to inlet holes near the roof on one side of the room, and on the other are a number of openings connected with an exit shaft. The cool and dry air (dried by the precipitation of the moisture when it is cooled) falls in a cascade into the room and lifts the warm air which passes out by the air-exit shaft. The walls of the room are lined with an insulating material and covered by glazed tiles, the windows are

double and the door is a thick one with rubber bands to ensure hermetical sealing these latter refinements undoubtedly added to the efficiency of the room but time has shown that they were unnecessary elaborations for the range of temperature that is required

Today air conditioning is altogether a much simpler affair single units are available that can be fitted into any window—in a matter of few minutes if the window is of the sash variety, and after some adjustment if it is a casement window. If the windows and doors are reasonably close fitting no special measures need be taken but, when the building is an old one the openings that will usually be found around the doors can easily be filled with felt and, if a curtain is hung over the door there will be very little interchange of air whenever the door is opened

The domestic units are designed to cool rooms of different cubic capacities a machine of about one horse power will usually cool a room of 4 000 cubic feet very efficiently. When the room has a very high ceiling

with the same floor space

For air conditioning the best room is one with a north aspect (in the

ape and if the  
re that the air  
only, that is  
e smoke laden

or otherwise obnoxious an exhaust fan may be advisable, if this is not

possible in it, as, until every object in the room has been cooled to the air temperature every surface is giving off heat that has to be absorbed

The cost of domestic air conditioning units is not prohibitive before the present war a machine sufficient to cool a moderate sized room of about 3 000 cubic feet cost about £100\*, and, where reasonably priced power electric current is available about a penny an hour to run. For the average tropical sojourner this is not a high price to pay for the very great benefits to health and efficiency that it provides or, to put it another way, it is better value to have a good night's rest than an extra whiskey and soda

For those who can afford slightly larger plants and are prepared to make structural alterations in their houses, it is possible to air condition three or four rooms in a house at a cost equal to that of

\* This was the price of a  $\frac{1}{2}$  'ton' (=  $\frac{1}{2}$  horse power) machine delivered in Calcutta. In the United States the price was about half this figure

two individual plants, especially if all the rooms are not likely to be used at the same time

Commercial houses that have introduced air-conditioning into their city offices have taken this step not as a luxury for their staff but as a sound business proposition

The temperature that it will be possible to provide in an air-conditioned room will naturally depend both on the machine and on the temperature and humidity outside. The comfort zone in a tropical country, where one is wearing thin clothes, is between 72° and 78°F with the humidity at 60 per cent, which correspond to 68.5° and 73.5° effective temperatures, respectively, and most efficient air-conditioning plants will usually achieve the latter temperature and humidity even in the most unfavourable weather, but even a temperature of 80°F with this degree of humidity (effective temperature 75°) will be sufficiently low to ensure a good night's rest for most people

Most one-room plants will bring the temperature down to very near the minimum level within an hour, and the more powerful house plants, when they are turned on to one room, in a matter of a few minutes, so that it is not necessary to run a plant continuously

nurseries, etc., are being extensively air-conditioned in some countries, but operating theatres. Complete air-conditioning is desirable even in temperate countries for modern anaesthetic gases and for other reasons. To ensure the comfort of the operating personnel, to increase their efficiency, and to reduce the chances of sepsis, it is almost a necessity

There is still much to be learnt about the patient's temperature requirements before, during and after operation, but some data, especially with reference to fatalities, have been collected, and, although it is clear that the requirements for the operator are not identical with those for the patient, it is reached in 10°F in warm

In 1940, as a result of extensive experiments in the United States, one hospital was rebuilt with the operating theatres completely air-conditioned, by means of two separate air-conditioning systems. One system serves all operating theatres using 100 per cent fresh air which is passed through disinfecting filters before being delivered into the room, the other system, which serves the operating rooms, takes in the excess air from the theatres and adds 10 per cent fresh air as needed, the balance being supplied by the theatres upon the

# DISEASES DUE TO THE DIRECT EFFECTS OF A TROPICAL CLIMATE

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**Introduction.**—When in extreme climatic conditions, other environmental conditions being optimal, the compensatory mechanisms of the healthy body fail to maintain the body within the normal physiological limits, climate may be considered to be the sole factor in the production of

Under this heading only pathological conditions that are solely or mainly due to climatic conditions will be included, but it must be remembered that other factors, e.g. a specific infection, may influence the symptomatology to a greater or lesser degree, and it will be convenient to consider also in this chapter conditions of multiple aetiology that are sometimes attributed to the climate

#### PATHOLOGICAL CONDITIONS PRODUCED BY THE HEAT RAYS OF THE SUN

The following clinical conditions are recognized as being produced by heat —

- A *Heat stroke*
  - (i) *Heat hyperpyrexia*
  - (ii) *Heat shock*
- B *Heat exhaustion*
- C *Heat cramps*

It would perhaps be appropriate to make some remark about the term 'sunstroke' which was commonly used until recently and which still causes a considerable amount of confusion, not only in the lay mind but amongst less well-informed medical personnel. The term was introduced when it was thought that the solar spectrum contained some mysterious ray, usually attributed to the ultra-violet end of the spectrum, that had a direct and detrimental effect on nerve tissue. There is no evidence for the existence of such a ray.

Another objection to the term is the fact that *coup de soleil* (literally 'stroke of the sun') has already been claimed by the French, for quite a different condition namely for what we know as solar dermatitis. It has been shown that the clinical conditions indicated by the term 'sunstroke' are all produced by heat effect on the body as a whole, though it is conceivable that localized heat applied to the brain or spinal cord might produce parallel conditions.

#### A *Heat Stroke*

**Definitions** — *Heat hyperpyrexia* may be defined as a condition in which, in order to keep the temperature down, it is necessary to use another term to in

#### Epidemiology

— ny means confined  
The heat stroke  
and Singapore is

lower than it is in a heat wave in New York, during heat waves in American cities the deaths attributable to heat amount to thousands per week. In the latter cities, the other environmental factors, both personal and general that is, the unsuitable clothes housing conditions, etc. enhance the effects of the climate on an unacclimatized population. Again, it is in the dry desert areas of North Africa Arabia, Iraq Iran and the North West Frontier of India that the condition is more frequently encountered than in the true tropics.

**Seasonal incidence**—It is of course in the hottest months of the year that most cases occur, and army statistics in India show that all heat hyperpyrexia occurs between May and September, half the cases occurring in June.

**Sex race habitus and habits**—Male adults form the bulk of the victims, mainly on account of the circumstances under which they have to work and live. In the army in India British troops are more susceptible than Indians and in the former the incidence is highest during the first two years of service after this there is another peak in the incidence curve at about 11 years' first two years is undoubtedly due to how to mitigate its effects and of and the second rise to increase acquired bad habits e.g. alcohol certainly a contributing factor.

The pyknotic individual is probably more susceptible than the asthenic, and obesity increases susceptibility.

Alcoholism and over-eating are detrimental. The teetotaler is undoubtedly at a great advantage in extreme conditions of heat, and alcohol should never be taken during the day in hot weather.

**Other environmental factors**—In addition to climate the other important environmental factors are unsuitable clothes, ill-ventilation and overcrowding (e.g. the historical 'black hole of Calcutta').

## Ætiology

**Physiology**—It heat balance (see p. body functions (100 calories an hour). The cooler immediate latent, that is, absorbed.

the temperature rises above this

Above this temperature all

humidity rises and the wet-bulb

temperature nears 98.4 F. this means of heat loss is also reduced to nil, and eventually the body temperature must rise.

Air movement and clothing are also important factors and can be considered together. Air movement will movement of air are temperatures above provided the air is cool.



usually increases total heat loss and clothes decrease it, but in extreme conditions of heat the reverse may be the case

temperature, humidity, and air movement, a single unit, the effective temperature, has been introduced (see p 8) An effective temperature of 97°F is about the upper limit of tolerance of the body, even naked and at rest

The following figures regarding the effect of different combinations of temperature, humidity, air movement, and work from various sources are worth quoting —

In still air at rest it is just possible to survive—

a temperature of 100°F when the humidity is 90 per cent

" " 120°F " " " " 40 " ;

" " 140°F " " " " 15 " ;

In each case the effective temperature is about 97°F

The body temperature will show a definite rise when the subject is—

at rest in moving air, at 93°F wet-bulb temperature\*

doing " still " 88°F

or doing moderate work in moving air, at 86°F wet-bulb temperature

or doing moderate work in still " " 78°F

The adverse effect of hot winds in a desert area is shown by the observation that at 128°F it is not possible to survive long in a wind of 20 miles per hour, whereas if the wind increases to 58 miles per hour long survival would not be possible even at 117°F

**Associated factors**—Of the *predisposing* factors, infection, usually—but not necessarily—with some organism that in ordinary circumstances might produce only a mild febrile attack (e.g. influenza, dengue, sandfly

this point might mean nothing more than that those who have had one attack are constitutionally ill-fitted to withstand high temperatures and are therefore likely to suffer again

From another point of view, infection and the taking of alcohol might be considered to be the *determining* or *precipitating* factors, both are potent factors in upsetting the finely-balanced heat regulating mechanism when it is working under the strain of adverse environmental conditions

### The Pathological Processes associated with the Breakdown of Heat Regulation

**A Hyperpyrexia**—A slight temporary rise of temperature under

ext  
wh  
or  
rise

sweating, and a vicious circle will be established. When the temperature reaches 108°F neuroglobin is precipitated and irreversible changes in the brain and cord occur

\*The discrepancy between these figures and those shown in figure 2 are dependent on the fact that the latter were based on patients subjected to artificial hyperthermia and that a different criterion for a definite rise in temperature has obviously been taken

*B, Circulatory failure (heat shock)*—In the attempt to get rid of

concentration, so that eventually there is an increase in the vascular bed, a decrease in the blood volume, and an increase in the viscosity of the blood. This will lead to a fall of blood pressure and circulatory failure. The recovery from such a condition is complicated by paralysis of the vaso-constrictor mechanism an expression of the general heat regulating failure. This circulatory failure is enhanced by the taking of alcohol and/or of a heavy meal, the latter causing splanchnic dilatation and a further increase in the vascular bed.

*C Electrolytic imbalance*—There is a continuous loss of chlorides and fluids in the perspiration, this fluid loss is usually replaced by pure water. It has been shown that the blood chlorides fall during the hot yrexia. There acid Marsh

	Cold weather	Hot weather	Patients suffering from heat effects
Blood sodium chloride mg per 100 ccm	494 $\pm$ 38	466 $\pm$ 29	448 $\pm$ 52 (mean of 45 patients)
Plasma bicarbonate millimols per 100 ccm	278 $\pm$ 0.26	254 $\pm$ 0.18	As low as 0.61
Blood lactic acid mg per 100 ccm	24 $\pm$ 6	30 $\pm$ 9	As high as 100

A better indication from the urine. Ever from a heavy cloud of to complete absence

Severe muscular cramps are a clinical manifestation of this condition (*vide infra*, Heat Cramp)

*D Sensation*—This is a most important factor in hyper- the of me blo ma prc rea possible

All these conditions are frequently produced in a single case of heat ill effects but at any one time there is usually emphasis on one particular process and the symptoms will vary accordingly

### Morbid Anatomy

There is usually a marked post mortem rise in temperature, but this will occur in other con of death from heat hyper and this may also seem seriously dehydrated

there may be a petechial rash. There is hyperæmia of all the organs, and particularly of the meninges which in certain instances also show œdema. The heart is stopped firmly contracted in systole, and the blood in the vessels is dark and viscid suggesting tar in appearance and consistency.

have been described,  
at such temperatures  
dies

### Symptomatology

*The onset*—When the patient is already under observation, the onset of the symptoms may be noted from the beginning, and if circumstances permit, the attack can usually be aborted. On the other hand, it may

*Early and prodromal symptoms*—The patient who is working up to an attack of heat hyperpyrexia will have a flushed and cyanosed appearance, his conjunctivæ will be red and his pupils contracted, and his skin will be intensely hot and dry, he may be drowsy, or uncomfortable and restless, and he will complain of a severe headache, of a constriction of the chest, often of frequency of micturition, and sometimes of a watery diarrhœa and vomiting. At this stage the pulse rate will be slightly increased and the temperature raised (but this may be due to the infection for which he is already under medical observation and it is mainly in such cases that the early symptoms will be observed).

*Second stage*—Nearly all the signs and symptoms of the early stage are increased, drowsiness or slight restlessness turn to marked hysterical excitement amounting to mania in many cases, the urine becomes scanty and if tested will show a distinct cloud of albumin, the pulse is now full and rapid and the respirations increased, and the temperature is beginning to mount rapidly. The knee jerks may be lost at this stage.

*Final stage*—This is very often the stage at which the patient is first seen. He is unconscious and often delirious, he has a burning skin, a cyanosed face, suffused conjunctivæ, bounding pulse, stertorous breathing, and the temperature may be to 108°F or higher. All reflexes are lost.

Stokes  
°F in

*Heat shock*.—The first sign of the effects of heat may be syncope, later to be followed by hyperpyrexia, on the other hand, syncope may be a phase of the general condition, or it may result from too vigorous treatment in the hyperpyrexial stage. There is collapse, vomiting and dyspnœa, the pulse is feeble, the systolic blood pressure falls to 70 mm. Hg or so, and the rectal temperature may be low, but quite often the temperature in the rectum still remains high.

### Diagnosis

— The fact that in the vast majority of cases it is the only other condition as well, and it is — However, if on a hot day a patient is unconscious with no obvious signs

## PREVENTION

of trauma vigorous treatment  
the collapse immediately  
conditions the most important  
vigorous action is indicated

### Prevention

Some of the ways of mitigating the effects  
above (see p 16 et seq)

The methods adopted will naturally depend  
circumstances For meeting any particular case  
in the production of heat stroke should be

of work and almost always to modify the climate  
to this last in the case of A R P workers who  
or rubber clothes and masks to protect the  
Work in particular should be graded to meet  
stances The soldier who is under training should  
in the heat of the day reduced in the hot sun  
an arrangement in which the soldier is  
the military authorities  
hot so that they  
this time or if the  
important part of  
imposed on the raw recruit

This brings one to the matter of acclimatization  
The general whose soldiers can fight in all climates  
great advantage in real warfare and in industry  
has to be done under adverse conditions Much  
the hours of work in trying circumstances very  
are reported to have arranged hot chambers  
work for gradually lengthening periods to  
withstand high temperatures before they go  
Africa The armies of the British Empire are  
being able to train many of their soldiers in hot

In mines in which work has to be done  
very hot miners are acclimatized gradually to  
cooler seams at first and then being transferred  
also by having their output of work in the hot  
been found that after long spells of leave return

During short periods of exposure to heat

suffering from shock—may not ask for water, and they must therefore not only be allowed as much water as possible but must be pressed to take it

The salt requirements will be from 10 to 20 grammes a day and more in special circumstances, this may be taken in the food or with the fluid y essential to increase the f sodium chloride to each makes an unpleasant drink ablets of salt with each during very hot weather

and should certainly not be taken during the day

When the question of salt intake is in doubt, the urine should be tested for chlorides, the urinary chlorides should not be allowed to fall below 0.5 per cent

**Test for chlorides in the urine**—The following simple test is a very useful one for the ward or clinical laboratory. The reagents required are potassium chromate 20 per cent and silver nitrate 29 per cent. The test is carried out as follows—

Ten drops of urine are taken in a test-tube and a drop or so of potassium chromate added. The mixture is well shaken. The silver nitrate solution is then added drop by drop the test-tube being well shaken after the addition of each drop. At a certain point the solution will turn brown, and remain brown after shaking. This is considered as the end point of the test.

The same pipette held at the same angle, preferably vertically must be used for measuring the urine and the silver nitrate. After it has been used for measuring the urine the pipette must be washed out first with distilled water and then with a small amount of silver nitrate. The potassium chromate is only an indicator and need not be measured accurately.

The calculation is made from the number of drops of silver nitrate added to 10 drops of urine before the colour changes to brown one drop representing 1 gramme of chlorides calculated as NaCl, per litre, that is if the 7th drop turns the solution brown the amount is 6 grammes per litre, or 0.6 per cent.

In a normal person, 8 to 10 drops will be added before the solution turns brown. In a dehydrated and hypochloræmic patient the brown colour will sometimes appear after the first drop, indicating that there are practically no chlorides present in the urine.

In every large hospital in a country where heat stroke is common, there should be an air-conditioned ward in which the temperature is kept within the comfort zone. This is particularly important in connection with industrial concerns where the work may entail subjection to temperatures even higher than that of the already high atmospheric temperature. Heat stroke subjects can then be admitted straight into such a ward and the lowering of their temperatures is considerably facilitated. Further, hospital patients showing the first signs of the failure of the heat-regulation mechanism can be transferred to the air-conditioned ward.

Much can be done in a hospital by keeping an intelligent watch on all febrile patients, and very frequently, even in the absence of an air-conditioned ward, it will be possible to abort the attack. Careful watch should also be kept on the urine to be sure that it contains the normal quantity of chlorides, and, if it does not, the salt intake should be increased.

In industrial concerns, the medical officer should see that the environmental conditions are improved as much as is practicable (e.g. by artificial ventilation), that the work of the new recruit is graded, that the health of the labour force is maintained at the highest level by other sanitary measures (e.g. anti-malarial), that the worker's nutritional requirements are adequately met, and that he is supplied with plenty of safe fluid throughout the day (*vide supra*).

### Treatment

The patient must be removed by the fastest means possible to a hospital or at least to some cooler place. If he is already in hospital he should be moved to an air-conditioned room—if there is one—or to the coolest place available.

All the physical means possible must be brought into action to bring down the temperature but drugs must be avoided at this stage. Hydrotherapy offers the best opportunities: cold baths, cold wet sheets, and ice packs, when ice is available, must be used freely, a hand or electric fan should be used to aid the cooling. Cool enemata and cool intravenous salines may also be employed, a note of warning regarding the former is necessary, because the rectum is the best temperature indicator from which one ascertains the point at which the cooling treatment is to be discontinued.

Massage is of great value in both the hyperpyrexial and the collapse phases. It is important to maintain the circulation in the former phase so that the cooled peripheral blood is conveyed rapidly to the internal organs, and in the latter, it will naturally form part of the treatment for shock.

The life of the unconscious person with heat stroke will depend on the early reduction of temperature so no possible means of lowering the temperature should be neglected. Once, however the temperature has been reduced to 102°F in the rectum vigorous measures should be discontinued, and the patient left in bed covered by a sheet or a light blanket, but he must be carefully watched to see that, (a) his temperature does not rise again, and (b) that he does not collapse and pass into a state of heat shock. It is by no means an uncommon experience for a patient—especially one whose heat-regulating mechanism has been upset by some infection—to see saw between hyperpyrexia and heat shock throughout the whole day, and when—as happened many times in Iraq in the writer's experience during the 1914-18 war—a number of patients in the hospital are doing this, the amount of work that falls on the staff may well be imagined.

For intravenous use, alkaline saline (sodium chloride—90 grains, calcium chloride—4 grains and sodium bicarbonate—160 grains, to a pint of water) should be given at a temperature of 60°F. This has the effect of lowering temperature, helping the circulation counteracting both the chloride loss and the acid increase, and combating dehydration, so that it helps to counteract all four pathological processes mentioned above. Warm (room temperature) intravenous alkaline saline will also be valuable in the collapse phase.

Drugs should be avoided as far as possible. No antipyretics must be given, and other drugs strongly contra-indicated are strychnine and atropine, the former because it will increase the neuro-muscular tonicity and exaggerate cramps, and the latter because it inhibits perspiration. Of the stimulants, caffeine, camphor and ether in oil, and coramine can be used, in that order. In cases of acute delirium chloral hydrate is the safest, and it may also be used for sleeplessness. Insulin of each) fail.

In patients in whom the blood pressure is high and there are signs of congestive heart failure, venesection should be considered, and, in unconscious cases with signs of cerebral irritation lumbar or cisternal puncture

may be advisable: In the former case, the blood should if possible be taken into citrate saline, so that if the state of the patient changes over to the collapse phase later, it could be returned to his circulation.

In the shock phase, whether it is the initial state or has followed hyperpyrexia, treatment is very much the same as for any case of shock, but the danger of pushing the patient over to the hyperpyrexial phase must always be kept in mind, and all measures that are aimed at increasing body temperature must be applied with great caution. The treatment will include nursing in the horizontal position, massage, possibly hot-water bottles, intravenous saline or 5 per cent glucose, and of drugs, cortin or the synthetic desoxycorticosterone acetate, pituitrin and adrenalin.

**Diet**—If the patient is conscious, he should be made to take fluids freely by the mouth, with glucose and sodium bicarbonate, and, if there is any chloride deficiency in the urine, sodium chloride up to two ounces in the twenty-four hours, must be given. The question of diet need not be considered for twenty-four hours and then a fluid diet should be given for a day or two before the patient is allowed to return gradually to his full diet.

**Convalescence**—This will depend on the gravity of the attack, but in any case the patient should not be allowed to return immediately to the environment in which the attack occurred, or to full work. He should, if possible, have a holiday in a cool and quiet place, live on a low diet, take no alcohol, and pay special attention to his personal hygiene including keeping his bowels well regulated. If it is thought advisable for him to return to work, he should at first return but his hours of work, and, if he is to return, the amount of work done should be

graded.

**Prognosis and sequelæ**—Prognosis will depend almost entirely on the rapidity and efficiency with which treatment is carried out. Rogers reported 83 per cent of deaths in patients whose temperature did not rise above 107°F, but when the temperature rises above 107°F or the patient remains unconscious for more than three hours the prognosis is bad, and, even if he recovers, he may suffer from the permanent effects of damage to nerve tissue. The factors that militate against recovery are previous hypertension, and the complication of some serious febrile infection, such as typhoid.

Sequelæ include long periods of low fever, headaches, myocardial weakness, enfeebled intellect, and sometimes dementia, according to Rogers the last occurs in about 10 per cent of severe cases of heat stroke. After an attack of heat stroke the subject is said to be much more liable subsequently to the effects of heat.

### B Heat Exhaustion

The epidemiology of this condition is naturally closely allied to that of heat stroke, but there are differences. For example, women are more liable to suffer from heat exhaustion than from heat stroke, and indolence is almost as likely to cause it as work. However, the male worker is also liable to heat exhaustion which is very often a prodromal stage of heat stroke, or it may be looked upon as a mild attack of heat stroke.

The ætiology is virtually the same, but there is more often a psychological element in heat exhaustion.

Some sojourners appear to suffer from a form of thermal instability, the defect in their heat regulation mechanism is probably congenital in

the majority, but in a few it appears to be acquired after some serious febrile affection such as typhoid or heat stroke

The symptoms include weakness and lassitude, headache, dizziness, diarrhoea and vomiting, mild cramps and sleeplessness. A rapid pulse, low blood pressure, and low fever will probably be the only clinical findings. Chlorides will usually be low and may be absent from the urine. In the case of the worker the first evidence may be that he faints at his work.

Some degree of anæmia will often be found and it must be looked upon as a contributory cause and due to some other ætiological factor possibly of dietetic origin.

In the thermal instability form the patient's temperature will rise to 102°F or higher every year when the effective temperature goes beyond a point say 85° at which most people are uncomfortable but able to compensate it. These patients are often diagnosed as enteric though they don't usually feel very ill and the writer has recently had a patient who was treated as enteric 5 times in 7 years. Many children's temperatures will always rise two degrees or so in the middle of the day in the hot weather without there being any discoverable cause.

Amongst patients with this condition there will be a good proportion of neurasthenics and malingerers but care must be taken that the genuine cases are not classed amongst these.

Treatment of the milder cases consists in removal of the patient from the surroundings that caused the condition, very careful investigation for some underlying disease, regulation of the diet and fluid intake—not forgetting the salt requirements, regulation of the bowels and finally the administration of some tonic mixture.

In the more severe cases the treatment will approximate to that given for heat stroke.

### C Heat Cramp (or Stoker's Cramp)

The excuse for allowing this symptom of the general syndrome of

musculature is directly connected with salt in the further loss

The cramps usually occur in the muscles that are not used. They may start either during work or some hours after work has ceased. As well as those of the fingers—especially the flexors—fore-arms, arms and legs, the muscles of the pelvic girdle and abdomen are sometimes affected. The involuntary muscles are never affected.

The muscle contracts to an iron like hardness and during the time

spasm may be started by active movement, by a knock or even by a cold draught playing on the skin over the muscle.



There is not necessarily much diminution in the urinary output, but there may be complete absence of chlorides from the urine. The blood changes include an increase of plasma protein, and of plasma potassium, phosphorus and calcium, and a marked diminution in plasma sodium. There is also an increase in cell volume percentage.

Prophylaxis has been discussed above. The most important feature is the provision of saline drinks. Ten grains to the pint makes a reasonably palatable drink, but this may not be sufficient. The taking of three 10-grain tablets with each pint of water is an additional precaution that may well be observed.

Treatment consists in giving copious saline draughts, and intravenous and rectal saline, if necessary. In severe cases, it may be necessary to relieve the cramps by giving morphia, or whiffs of chloroform.

The similarity of this condition to hyperventilation tetany has been pointed out recently, but it seems unnecessary to suggest that the physiological hyperventilation which occurs in a hot climate is likely to be the cause of the cramps when there is a much better explanation.

Morbus Britannicus is an allied condition that was at one time common amongst British sailors. It was due to loss of chlorides in perspiration and vomitus, it is usually, but not necessarily, associated with a hot climate. It received its name from the fact that Scandinavian sailors who lived on salt meat seldom suffered from it, whereas it was common amongst British sailors who lived on fresh meat.

The abdominal muscles are usually affected—because of the important part played by vomiting—and the condition often simulates an acute abdomen.

#### PATHOLOGICAL CONDITIONS PRODUCED BY THE ULTRA-VIOLET AND LIGHT RAYS OF THE SUN

One of the main effects of the ultra-violet rays is the conversion of the cholesterin of the skin into vitamin D. The pathological condition is therefore doubtful if it could ever occur.

Solar dermatitis—the French *coup de soleil*—is a condition that is actually produced by the ultra-violet rays though the other sun's rays probably play some part in sensitizing the skin to the effects of these rays. After over-exposure to the sun's rays, the first effects will appear in about two hours and the maximum effects in about six hours. At first there is erythema, then a hyperæmia of varying intensity up to a serious congestion with œdema which may be followed by blistering, there is in any case a superficial necrosis of the epidermis, which eventually separates, as in a burn of the first degree, leaving the deeper layers of the skin exposed to the risk of secondary infection. The immediate inflammatory reaction may be a serious one causing severe pain locally, high fever, and toxæmia, even more serious results may follow secondary infection. Thus, though the condition is usually treated lightly and often jokingly, a severe sun-burn may have a fatal result.

The parts most likely to be affected are the uncovered areas of skin on which the sun's rays fall vertically, the upper part of the forehead, the nose, and the malar eminence, the back of the neck and shoulders, the backs of the hands and the dorsa of the feet, and the knees and the fronts of the thighs if the exposure was in the sitting posture. A single layer of clothes, even a thin handkerchief, will usually give complete protection.

Sun-burn is usually the effect of direct sunlight, but serious sun-burns will also result from the reflection from snow or desert sand, and on a dull day the same effect may be produced by reflection from the clouds, so that care should be taken not to leave a sensitive patient on the verandah on such a day. In the case of snow-burn the lesions will be mainly on the neck, the chin and lower part of the face.

In specially sensitive individuals an urticaria sometimes develops on areas exposed to the sun, the condition has been called 'urticaria solaris'. Rays between 3800 and 5,000 Å are thought to be responsible for this somewhat rare effect (Arnold, 1941).

Frequent exposure to the sun's rays will eventually lead to the deposition of pigment, which gives some protection to the skin during subsequent exposures. Whilst the rays between 2800 and 3,100 Å are the most potent in the production of erythema the longer, light rays are more active in the production of pigment. Repeated irritation from over-exposure to the sun's rays will produce keratosis and a pre cancerous condition which may eventually develop into rodent ulcer or epithelioma conditions that are common amongst men of European descent living open-air lives, in Australia for example.

The natural pigment of the dark-skinned races protects these subjects to a large extent from these effects, and amongst fair-skinned races the brunette is less susceptible than the blonde (*vide supra*). Certain substances sensitize the skin to the effects of the ultra-violet rays, for example,

Amongst drugs, the heavy metals that are used for injection, *e.g.* gold, and substances that have fluorescent properties *e.g.* dyes, such as trypanflavin, used in the treatment of brucella infections cause sensitization.

Prevention does not present any great difficulties, a single layer of clothing even a silk handkerchief, for example, or a thin layer of any oil will protect the skin from sun-burn. Ordinary yellow vaseline, or 2 per cent tannic acid and 10 per cent castor oil in spirit as a prophylactic paint, are quite as good as any of the more expensive preparations that are advertised. Usually the main difficulty is to keep the application from being washed away by the sweat, or absent-mindedly wiped away when the face is mopped.

The treatment of sun-burn is purely palliative, cold cream or calamine lotion are probably the best substances to apply. The more serious lesions must be treated as burns, with 2 per cent tannic acid and 10 per cent silver nitrate spray, with the triple dyes, or with whatever is the treatment indicated by the distribution of the lesions.

Light stroke or severe form of sun-headache is a common and sometimes serious syndrome amongst newcomers to the special environmental conditions that produce it. In this case, it is in almost every instance the reflected light rays from snow, desert sand, bare baked earth, and water surfaces, rather than the direct ones that are mainly responsible.

The symptoms produced are intense headache, vomiting, prostration and fever. Much of the so-called 'sunstroke' of a few decades ago was undoubtedly this condition and today the layman still attributes his symptoms to failure to keep his local effect on the retina is a considerable and in extreme cases is usually temporary and from complete recovery may be confidently expected.

The direct and indirect glare from the tropical sun undoubtedly plays a part in the production of night-blindness, though this condition is more often due to psychological causes. Strong light breaks down the visual purple in the retina which is again formed with the aid of vitamin A. When the diet is deficient in vitamin A night-blindness has its symptoms of vitamin-A deficiency: yellowish foam-like patches on the cornea (xerosis) and keratomalacia (softening of the cornea). Conditions such as hookworm disease and malaria, also increase this tendency to night-blindness.

Prevention consists in the wearing of suitable tinted glasses. In the green tropics Calobar-D lenses are suitable for general use and it is a mistake to have glasses unnecessarily dark, as this leads to eye strain when objects have to be viewed accurately, but in desert areas much darker glasses may be necessary.

Treatment consists in rest in a darkened room. Phenobarbitone should be given to relieve the severe headache, and for the prevention and treatment of night-blindness with the addition of vitamin-A (the fish-liver oil, the vitamin proper, and red-palm oil or pre-vitamin A) from which Any associated anaemia should

be treated appropriately.

## OTHER CONDITIONS THAT ARE ATTRIBUTED TO TROPICAL CLIMATE

### Tropical Anaemia

It is not only during the tropics but also in the tropics and that the home-returning sojourner has ceased to drink nightly a glass of port wine—the hæmatinic value of which is incidentally more than questionable—to counteract this thinning as his ship enters temperate waters. The hæmoglobin content of the blood of the healthy sojourner is higher than of people of his class in the tropics. The reason for this should be sought and with dietetic deficiency. This also certainly not lower.

### Tropical Neurasthenia

It is a condition that has come into general to it and certainly Many practitioners amongst their patients and have labelled them tropical neurasthenia, as far as we know, no series of cases has been studied and no scientific data regarding the most commonly associated physical conditions or even the environment in which tropical neurasthenia most frequently occurs has been collected.

The ætiological factors can be grouped under the following heads and if the author were compelled to assign the degrees of importance to these factors he would give the percentages as indicated below —

(a) Physical—disease or fatigue	50 per cent
(b) Heredity	20 " "
(c) Social and environmental conditions	15 " "
(d) Mental strain—overwork and over-responsibility	5 " "
(e) Alcoholism and drug addiction	5 " "
(f) Climate <i>per se</i>	5 " "

(a) *Physical*—Under the list The commonest followed by a condition of discomfort The patient often he has not

His attention becomes centred on his bowels and his diet, in his over-anxiety to rectify the bowel disorder, he often remains on a low fluid diet for long periods and this leads to specific malnutrition of the bowel wall, stasis, fermentation and dilatation a condition of dysfunction of the small intestine, which may or may not be associated with ulceration of the large gut, and anæmia

Unsuitable, indifferent and monotonous food served in depressing surroundings that is liable to be the lot of the isolated bachelor will often result in loss of interest in food and the necessity to stimulate this by alcohol, this sequence again will lead to a state of undernourishment

Debilitating febrile conditions, such as malaria, also predispose to neurasthenia, especially when frequent relapses occur, and both dengue and sandfly fever are particularly liable to lead to a state of depression and mel- id in suicide  
Finally, emetine, in the form of tors in producing drug after the cinchona alkaloids, in tropical practice, but it is certainly the most abused

A phase that follows a run of ill-health is the patient's fear of being ill again and this may be accompanied by worry that he is not doing his work and earning his pay, or, more egotistically, that he will lose his appointment This phase is usually much more highly developed in the married man with children

Fatigue may result from physical overwork, or the mistaken idea that exercise is the cure for all ills

(b) The influence of *heredity* will not be avoided by sending the patient abroad, as the heads of families—ill-advisedly encouraged by their family doctors—sometimes appear to think, or perhaps only hope This expedient often presents an easy way of getting rid of a grown-up 'problem child'. Or, the weaker type of man hopes to escape from the speed, bustle, and competition of life in the west by coming out to the

tropics, where, however, he finds that other qualities, which also quite frequently he lacks, are necessary, and again he has to face the fact that he is a failure\*.

Medical men who pass recruits for the tropics should pay particular attention to this aspect of their examination.

(c) A young man comes out directly from school or college—this applies to both sojourners and educated natives of the country—and finds himself in some isolated spot many miles from the nearest potential

On the other hand if he is happily married and has children, he has their illnesses and that of his wife to worry about as well as his own. Finally, unhappy marriages are a very common cause of neurasthenia in either or in both partners.

(d) *Mental strain* is a common cause of neurasthenia in any climate. However, in the tropics, young and/or inexperienced sojourners are more often suddenly thrust into positions of considerable responsibility, or of special danger, for which they are not really fitted, and the experience is sometimes too much for them.

(e) *Alcoholism* is probably more often a manifestation, or rather a symptom, of an unstable physical, this sub-  
he victim  
in a neurasthenic condition.

*Drug addiction* is not common in sojourners, but cannot be excluded as a cause of neurasthenia.

(f) Probably the only direct effect of climate per se in this capacity, except in very extreme conditions, is by interfering with rest at night.

Neurasthenia are naturally different in men and women, and in an even more important part, separations from children are also more prominent factors, and sexual neuroses are probably more common in women.

Actual fear of servants, native neighbours, snakes, insects, etc., is probably a factor more or less confined to women. Idleness and boredom replace overwork as factors. Alcoholism is probably less common amongst women but cannot be excluded, and is to some extent replaced by 'chain smoking'.

**Symptoms**—These do not differ materially from those exhibited in a temperate climate, and will vary with the aetiology. Headaches, sleeplessness, inability to concentrate and loss of memory, indecision—even in such an unimportant matter as to whether to use a spoon or a fork—loss of

\* On this subject, Professor Culpin (1939) says 'there is a selective tendency at work by which home-misfits vainly seek a new environment for their mal-adjusted personalities'.

emotional stability, hypochondriasis, and acute depression—even to the extent of committing or attempting suicide—are some of the common symptoms. Frequently there will be tachycardia, a subnormal or an unstable temperature (i.e. one permanently raised about a degree above normal in the hot seasons), a blood pressure on the low side, and sweating of the palms. Reflexes may be exaggerated.

*Treatment.* The essential feature of treatment and perhaps more

A sympathetic appreciation of all the patient's symptoms is essential but care should be taken not to be too mysterious about these, or he may suspect that he is suffering from some serious condition which is being hidden from him.

Hypochondriasis often merges into neurasthenia and it is sometimes a good plan to send a patient to some medical institution for a 'thorough investigation'. This will have a double effect, some unsuspected underlying cause, e.g. a protozoal or helminthic infection, gastric dysfunction or gall bladder infection, nasal sinuses, tonsils or teeth infection, an error of refraction, or even some easily corrected blood dyscrasia may be found, or, if nothing is discovered as a result of various investigations, the patient's confidence in his own health may be restored. Naturally, whenever possible, these investigations should be carried out by the doctor himself, capital should be made out of any discovery however trivial and very thorough treatment given in the case of any important finding.

The insomnia should be treated first by investigating the environmental

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d  
a

Drugs will usually be necessary and should be given in such a form that the dose cannot be gauged accurately by the patient, that is, either in mixture or in cachet form. A large and effective dose should be given at first and, when the habit of sleeping is acquired, the dose can be reduced.

R Chloral hydrate	..	gr xv	Spiritus ammoni aromaticus	℥ss
Potassi bromidi			Syrupi auranti	3i
Ammoni bromidi		℥ gr x	Aquam chloroformi	ad 3i
Sodii bromidi				

To be taken at bedtime, with a dose put ready to be taken 3 to 3 hours later if necessary.

Phenobarbitone gr 3 and paraldehyde 3i are alternatives. Later, the chloral hydrate in the bromide mixture can be replaced by aspirin gr x, and this sleeping draught continued for some time.

If no cause for the headache can be found, APC powder (aspirin gr x, phenacetin gr iii and caffeine gr ii), Veganin, or Saridon should be tried first, and if these fail stronger drugs such as phenobarbitone may have to be used.

Whilst sedatives are usually indicated at first, later, when the insomnia is under control and there is some general improvement in the mental condition, tonic mixtures should be prescribed. Some of the proprietary mixtures, e.g. metatone, are useful in this connection.

A change of environment to a cooler climate is the obvious treatment for a neurasthenic, but this measure should not be resorted to until some attempt has been made to cure or counteract the underlying cause, or causes. If the patient is a sojourner and his home leave is due, he should certainly be sent home, but, if not, a month or two in a suitable hill station, or a short sea trip, preferably away from wife, or husband and or children, as the case is, may be sufficient, but care should be taken to choose a place where the patient will find suitable amusement and exercise, it is no help to a neurasthenic with dypsomaniacal tendencies to send him to a hill station to spend his time in the club bar!

### Tropical Liver

This popular term describes a condition, probably commoner in the tropics than in temperate climates, that is not easy to define in medical terms.

Heavy functional demands on the liver lead to a condition of hyperæmia, which is within physiological limits at first but later becomes a pathological congestion, as well as being a troublesome minor malady, the condition is of importance because it predisposes to hepatitis and liver abscess.

These conditions lead to a high degree of para-  
 . . . also  
 . . . dominate  
 . . . Up to a  
 . . . produced  
 . . . alcoholic  
 . . . in fact,

In the indigenous tropical resident, on the contrary, an excessive carbohydrate diet with a low-protein intake and vitamin deficiencies lead to a similar condition, and here again parasitic infections are very important.

The main symptoms are headache, dirty tongue, loss of appetite, general tiredness, sudden attacks of sleepiness, and a feeling of weight below the diaphragm. There is usually some tenderness in the liver region and possibly slight enlargement, a general unhealthy coloration of the skin, and sometimes an icteric tint of the sclerotics.

Prevention consists in adjustment of diet and habits, and an occasional dose with sodium bicarbonate in a glass of water. The regular taking of salts in the morning is a habit that is very easily acquired and is not a good one, as it is very liable to lead to constipation.

Treatment should first be directed at the elimination of any parasitic infection. As a general measure, after the diet has been adjusted, divided doses of calomel should be given at night, gr.  $\frac{1}{2}$  every half hour up to six doses, followed by salts in the morning, and then for a week a nightly pill.—

R. Pilulae hydrargyri .. gr iv  
 Extracti aloes .. gr ii  
 Extracti hyoscyami succati .. gr i

valuable alkaloid, but it is a very dangerous drug when it is abused.

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 How-  
 to con-

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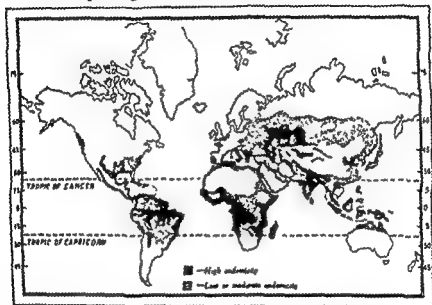
**Introduction** — Malaria is by far the most important disease in the realm of tropical medicine. In the distant past it has caused the decay of empires, and in the near past the failure of the best conceived military campaigns, in our own times it has led to the abandonment of many engineering projects and has delayed innumerable others. Of all diseases except possibly the common cold it is the most widespread, it is the cause of the greatest economic loss, and it has the highest incidence in nearly every tropical and sub-tropical country. It has been subjected to a greater amount of study than any other tropical disease and a vast amount of knowledge has been accumulated about it, yet there are many lacunæ in this knowledge, it is the most easily treated of all serious diseases yet it is a disease in which the treatment is most often neglected, it is controllable and yet so seldom controlled, and it therefore still provides the greatest problems to the sanitarian and dominates the practice of the clinician in the tropics.

almost every country in the world, but mainly in the tropics. It is caused by a plasmodium, a protozoon of the order *Hemosporidia*, which is transmitted from man to man by mosquitoes of the genus *Anopheles*.

## EPIDEMIOLOGY

Epidemiology means literally the science of epidemics, or it can be defined more liberally as the collection and the study of observed facts regarding the behaviour of disease in relation to man. In the case of malaria, these facts have been observed and the data regarding them collected from the time of the historian Herodotus and probably earlier, and today are still being accumulated.

Figure 4. Distribution of malaria throughout the world



Much of these data were collected in total ignorance of the cause of the disease and how it was transmitted from man to man, it was, however, the careful study of these accumulated facts that led, after journeys along many false trails, to the discovery of the true etiology of malaria, and, conversely, it is our knowledge of this etiology that has allowed us to explain many of the observed facts in its epidemiology, the reasons for which were hitherto obscure. It is therefore logical first to summarize the epidemiological data, then to state what is known about the etiology, and finally to attempt to correlate the two and explain, as far as our present knowledge goes, what are the factors that control the incidence of malaria.

The data that have been accumulated can be arranged under a number of headings:—

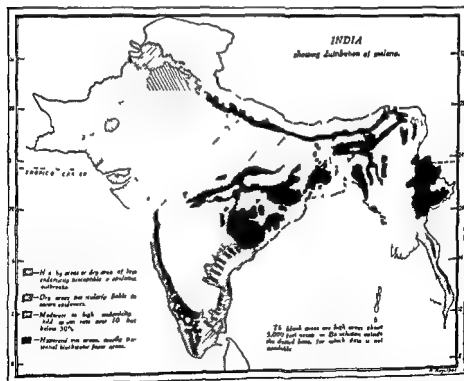
**Geographical distribution.**—This is world-wide, malaria occurs in the tropical, sub-tropical and temperate zones, though it is commoner in the former than in the latter. It is found in all the most densely populated territories, and in some of the most sparsely populated, and at altitudes which it has been reported (the incidence at high altitudes is probably a matter of temperature)—and that certain islands in the Pacific, e.g. Tahiti, Samoa, Fiji, Hawaii, are still free from the disease, the word 'still' is used deliberately, because at one time other islands, Reunion, Mauritius, and until quite recently Barbados, were reported to be free from malaria.

Each of the malarial fevers caused by the four different species of parasite (*viz*) has a different distribution. The widest is benign tertian whose domain extends from  $60^{\circ}\text{N}$  to  $40^{\circ}\text{S}$ \*, quartan has a patchy distribution in all three zones, but malignant tertian is essentially a malaria of warm countries, is limited by the  $70^{\circ}\text{F}$  summer isotherm, and does not occur beyond  $42^{\circ}\text{N}$ . The malaria caused by *Plasmodium ovale* has a sparse and patchy distribution as yet ill-defined.

The world map shows that malaria occurs in almost every inhabited country on the Canada and the New Zealand, always been.

The distribution in India and Burma is shown in figure 5

Figure 5



In any country, district, or large area where most always localities which are ly, in countries in which malaria

\* Beyond  $45^{\circ}\text{N}$  and  $25^{\circ}\text{S}$  it can scarcely be considered a disease of public health importance there is in fact not very much inhabited land as far south as  $40^{\circ}$

■ rare, there are localities which are intensely infected, even in a small town or village, there are often considerable differences in the malaria in different parts and one can go further and say that, in a single building, it may be found that those who live on the ground or lower floors are subject to malaria, whereas on the top floors the residents may be comparatively free. It is thus essential, when studying malaria in any locality, to note carefully where the people live who are most subject to the disease.

Observations of this kind were made in the earliest historical times. Herodotus (5th century B.C.) referred to the dangers to health of build-

malarious countries with the result that many thousands of people have died of malaria.

Seasonal incidence and variation from year to year.—There are few places in which malaria occurs with equal intensity throughout the year. Such variations are found even near the equator where, though there is little seasonal change in the temperature, other factors come into operation. On the whole, however, the seasonal variation in malaria is less marked the nearer one is to the equator. The seasonal incidence also depends to some extent on the malaria species that is prevalent, and where more than one species is to be found in one place, which is usually the case, the malaria may be caused mainly by one species at one time of the year and another at another time (see figure 6). Malignant tertian malaria is often called *æstivo-autumnal*, for in many European countries it only occurs in the summer and autumn, and in all countries where there is a distinct cold season, the incidence of malignant tertian drops almost to zero during this season.

Each country and even each district has its own seasonal malarial curve, in most places, this will show only minor variations from year to year, in its general shape, even though the variations in the height of the curve may be considerable.

It is usual to consider malaria as endemic or epidemic, but, even in those localities in which it is endemic, the incidence of the disease is subject to periodical exacerbations. In the epidemic regions, the epidemic does not take the form of an introduction of malaria into a place where it did

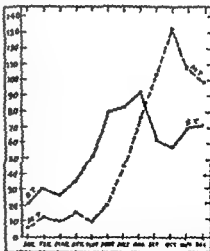


Figure 6. In June, 80 per cent of the malaria is benign tertian, in October only 30 per cent of the malaria is benign tertian (Northern India).

(Action II W., 1910)

not exist before—as in the case with cholera, for example—but of a sudden and often very dramatic flaring up of malaria in an area where it occurred in a mild form before, but was normally a disease of little public health importance during most of the year, in such an area, though the individual conditions that affect malarial incidence may not vary much from year to year, it is the concatenation of a number of events that brings about a state of affairs favourable for an epidemic, cf Sydenham's epidemic constitution. Epidemics tend to occur in cycles of a definite number of years.

In India there are two main types of malaria seasonal curve the Punjab type and the Bengal-Assam type. In the former, the incidence is low during most of the year and with the onset of the rains there is a sudden rise which will in certain years amount to an epidemic.

These epidemics have been studied by the health authorities and it has been shown that it is often possible to foretell whether it will be a normal or bad year for malaria. This information is very valuable.

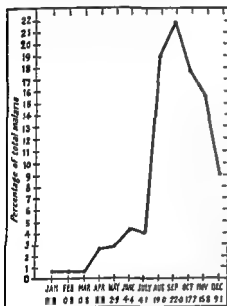


Figure 7 Seasonal malaria curve in Delhi  
(Knowles and White 1930)

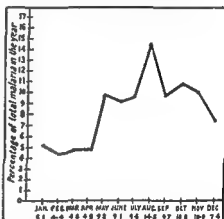


Figure 8 Seasonal malaria curve in the Assam Valley  
(Knowles and White 1930)

because it enables these authorities to set in motion the special organization for dealing with the epidemic immediately it arises. In the endemic areas, e.g. in Assam and Bengal, the disease is perennial, but the curve shows a steady rise in July and August and reaches its peak in about November, after which it falls fairly rapidly.

A minor spring rise in the incidence curve has often been noticed, particularly in benign tertian areas in Europe.

These endemic areas are not entirely immune from epidemics, as was shown recently by the Ceylon epidemic of 1934/1935.

In studying malaria in a locality an attempt should be made to prepare a seasonal graph from past records if they are available or plotted separately. The larger the the better, and if only one year, or

a small number of years, are included, an attempt should be made by careful local enquiry to ascertain if the year or years were 'normal' as far as malaria was concerned

**Age and sex incidence**—Individuals of all ages are subject to malaria. There have been a number of instances of congenital infection reported, but this is not a normal mode of transmission of the disease it will be referred to again later. Children are particularly liable to infection, and in them it usually takes a serious form. In a malaria-infected community, children are important for two reasons, firstly, they react to malarial

of the disease

The age composition of a community is thus an important factor in normal epidemiology. If children form a large proportion of the population malaria will be more difficult to control.

**Race and caste**—Persons of all races seem to be equally susceptible to infection, provided the circumstances in which they live are the same, though there are considerable differences in the morbidity caused by malaria. There are many instances in which the indigenous population appear to be unaffected by the disease, whereas foreigners, of whatever race, become seriously ill when infected, one of the best examples of this is provided by blackwater fever, a malarial disease (*vide infra*). It has also frequently been observed that any disturbance of the population, for example, the migration of a large number of persons into another country, may not only lead to a high incidence of malaria amongst the immigrants but also to a great exacerbation of the disease amongst the indigenous inhabitants. This is a recognized principle of herd immunity that is certainly applicable to malaria.

The racial composition of a population and more especially any changes that have taken place recently are therefore important facts to be noted.

infected, who has to make long marches in trying circumstances is very liable to suffer from malaria, either an initial attack or a relapse. Any severe physical strain or trauma, e.g. surgical or obstetric operations, x-ray applications to the spleen, or sudden cold, may precipitate an attack in an infected subject.

The economic factor is one of great importance in determining the development of immunity to malaria. It has been shown frequently that when the malar epidemics



not exist before—as in the case with cholera for example—but of a sudden and often very dramatic flaring up of malaria in an area where it occurred in a mild form before, but was normally a disease of little public health importance during most of the year, in such an area, though the individual conditions that affect malarial incidence may not vary much from year to year, it is the concatenation of a number of events that brings about a state of affairs favourable for an epidemic, cf Sydenham's epidemic constitution. Epidemics tend to occur in cycles of a definite number of years.

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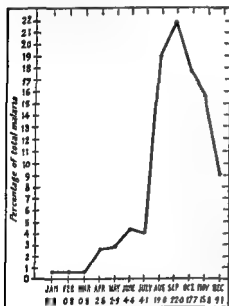


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In studying malaria in a locality an attempt should be made to prepare a seasonal graph from past records if they are available or failing that from current observation. If possible the malaria caused by the three different species should be plotted separately. The larger the number of years included in these data the better and if only one year, or

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The racial composition of a population and more especially any changes that have taken place recently are therefore important facts to be noted.

**Occupation habits and economic status**—Numerous observations have been made under this heading, back to the time of the Roman historians who pointed out that in certain malarious districts it was dangerous to walk out at night and loiter by the water's edge. The danger to soldiers carrying out night operations or standing guard at night, and to police on night duty has frequently been observed. Again the soldier previously infected, who has to make long marches in trying circumstances is very liable to suffer from malaria either an initial attack or a relapse. Any severe physical strain or trauma *e.g.* surgical or obstetric operations or ray applications to the spleen, or sudden cold, may precipitate an attack in an infected subject.

The economic factor is one of great importance in determining the development of immunity to malaria. It has been shown frequently that when the economic condition of a rural population in particular, improves the malaria loses much of its morbid potentialities. Conversely, severe epidemics have often been correlated with an economic depression.

The best example is the Roman Campagna which once harbouring a flourishing agricultural community, was through misgovernment allowed to degenerate at intervals into a deadly malarious swamp for nearly two thousand years, but has now reacquired its former agricultural prosperity and malaria has disappeared.

Other examples of how development is are the fen districts in England the many Lower Egypt and in India the areas of the Cauvery and the Godavari. Conversely Corsica is often quoted as a country in which agricultural deterioration has led to a great increase of malaria, and the Ceylon epidemic followed a period of economic depression.

It is thus obviously important to collect full data under all these headings.

### ÆTIOLOGY

**Historical**—The early theories regarding the cause of malaria were numerous. The word 'mal-aria' (bad air) is evidence of one of the earlier theories not unreasonably founded on the fact that the disease prevailed in low marshy country where the poisonous miasma arose from the ground at night. Another theory was connected with water and it has been suggested that the first Roman aqueducts were built on account of the prevalence of fever in Rome; the partial success of this measure would be accounted for by the reduction of other water borne fevers.

Night flying biting insects came under suspicion very frequently and Herodotus referred to the use of what we should call mosquito nets by the Egyptians.

Laveran described the malaria parasite in 1880; this discovery was developed considerably by the Italian workers Marchiasava, Celli and Golgi who demonstrated the different species and associated these with the various clinical pictures. This work was hampered by the absence of a suitable stain for the parasites and the perfection of a staining technique by Romanowsky in 1891 considerably aided future investigations.

This discovery of the causal organism opened up the field for the investigation into the mode of transmission of this parasite from man to man. It is difficult to trace the germ of an idea to its origin. Credit is due to the Jules Vernes and H. G. Wells of medical science who produce many excellent and also it should be remembered many false ideas. It is however the man who has the perspicacity to sort the grain from the chaff (or who the cynics will say is lucky enough to follow the right trail) and develops the ideas that usually gets and probably deserves the most credit. When Manson first turned his attention to the problem of the transmission of malaria the idea of an arthropod carrying a disease was new but not entirely new for as early as 1869 Fedtchenko suggested that dracontiasis was transmitted through the medium of cyclops (an

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to be questioned. It has been  
causes malaria whilst at the  
uses poverty with its sequel

Hackett (1937) has questioned whether malnutrition does cause malaria and adopts the view that the reaction is all in one direction namely malaria causing poverty and malnutrition. This view is supported by Covell (private communications).

In support of this view, these very widely experienced malarialogists quote much suggestive data including the fact that the healthy and well fed British soldier is very susceptible to malaria which in him quite often takes a fatal course.

This and most of the other examples they quote do not in any way run counter to the views of the writer regarding malnutrition and malaria; he believes from medical and pathological as well as from epidemiological experience that nutrition affects not the non immune patient's immediate response to a malarial attack but rather the way that immunity develops in the individual subjected to repeated attacks of malaria.

observation subsequently shown to be correct) Ten years later, Manson discovered filarial embryos in the mosquito, and from this time onwards he probably nursed the idea that malaria was also in some way connected with the mosquito In 1883 King in America published a paper containing a well-reasoned justification for the mosquito hypothesis Manson interested Ronald Ross in this subject and in 1897, working in Secunderabad Ross discovered the pigmented bodies (oöcysts) in the stomach wall of the dapple-winged (anopheles) mosquito

The causal organism—This is a protozoal parasite of the class Sporozoa the order Hemosporidia, and the genus *Plasmodium* There are four recognized\* species of *Plasmodium* that infect man in nature, *Plasmodium falciparum* that causes quartan in *P. ovale* that causes a malaria parasite, *P. kn* causes transient malaria, but it is doubtful if this occurs in nature

There are undoubtedly a large number of 'strains' of parasites of

induced by infection with the Madagascar strain, and the Rome strain of malignant tertian is particularly resistant to treatment

In one locality there are probably many strains, this is indicated by the fact that, in a very malarious place, it may be many years before the children acquire immunity to all the malarial strains in the locality

The life cycles of the four species of human plasmodium are practically the same

There are two phases in the life of the malaria parasite, an intra-corporeal phase in the intermediate host—man, and an extra-corporeal phase in the definitive host—the female mosquito, and two cycles, the asexual and the sexual These phases and cycles do not correspond with each other

The forms of the malaria parasite that are found in man—The ring form, which is seen in a Romanowsky-stained film as a pale blue disc with a red chromatin dot at the edge lying within a red blood corpuscle, is at first very small but rapidly dark pigment (hæmazon), fills practically the whole cytoplasm, its chromatin is into masses, the fragments in size now tend to become arranged evenly throughout the cytoplasm and

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*P. vivax* from 14 to 24 and in *P. falciparum* the number is more variable, from 12 to 32. The merozoites then attach themselves to and eventually enter red cells where they again start the asexual cycle or they may develop into sexual forms, the male and the female gametocytes. The fully developed gametocyte fills the whole cell like the schizont, but the gametocytes of the three malaria species have distinctive characteristics. The most distinctive is the crescent form of the malignant tertian parasite, the male gametocyte is long and slender with a large nucleus and the pigment scattered throughout the cytoplasm whereas the female is stouter and shorter, and has a small nucleus with the pigment distributed around it. The *P. vivax* tertian and *P. malariae* gametocytes are more or less globular in the former the nucleus is an irregular mass and in the latter it takes the form of a rod or band. (Further details of the morphology of the different species will be given below, see DIAGNOSIS.)

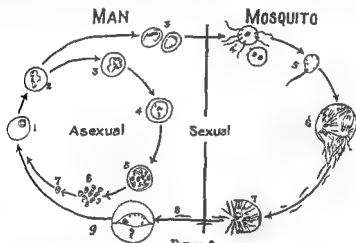


Figure 9

## Asexual cycle

- 1 Ring form
- 2 Growing trophozoite
- 3 Trophozoite
- 4 Schizont
- 5 Fully grown schizont rosette form
- 6 Burst rosette
- 7 Merozoites

## Sexual cycle

- 1 Ring form
- 2 Growing trophozoite
- 3 Gametocytes ♂ and ♀
- 4 Flagellate bodies and gametocyte ♀
- 5 Fertilized gamete (Ookinete not shown)
- 6 Oocyst—in stomach wall
- 7 Sporozoites—in salivary gland
- 8 Free sporozoites
- 9 Exo-erythrocytic stage

in mosquitoes

**The asexual cycle**—The cycle—ring, schizont, rosette merozoite, and again ring—lasts 48 hours in malignant tertian and in benign tertian and 72 hours in quartan malaria. This fact determines the periodicity of the fever: the rigor corresponds to the bursting of the rosette. This asexual

cycle leads to the multiplication of the parasites within the host, but, if it were the only form of development, there would be no chance of propagation of the species beyond this individual host, for the particular parasitic brood would end its existence in this host, they might kill him, or they might be destroyed by the cellular or humoral reactions of the host's tissues, therefore, for the continuance of the parasite's existence the sexual phase is necessary (see figure 9)

On the other hand the sexual parasites, the gametocytes, have no future within the individual host in which they are formed, for they are capable of no further development. Their future lies only in the mosquito, and if they are not taken up by a suitable mosquito, after living for about three weeks in the blood of their host, they die

**The sexual cycle**—When a mosquito vector feeds on an infected man, it takes in a number of malaria parasites. Any asexual forms will die, but the mature male and female gametocytes continue to develop in the stomach of the mosquito, from the male gametocyte a number of flagellate bodies separate and eventually enter a female gametocyte which they fertilize, the fertilized gametocyte, or gamete, undergoes development and becomes an ookinete an elongated body with considerable powers of penetration. The ookinete penetrates the endothelial lining and buries itself in the wall of the mosquito's stomach where it develops into an oocyst. These oocysts can be seen as glistening bodies in the blood. They are 40 to 80  $\mu$  in size. The sporozoites enter the body of the mosquito as motile bodies and find their way into every part of the body of the mosquito except the ovaries but in the salivary glands they find a particularly suitable medium for continuing their existence. Once the sporozoites have reached the salivary glands, whenever the mosquito takes a blood meal the sporozoites escape with the salivary material and enter the body of their new host.

The time taken in this phase in the mosquito is variable, according to the conditions, the shortest time is probably about 8 days but under adverse conditions, particularly in the cold when the mosquito is hibernating it may take many months. The average time in moderately favourable circumstances is usually looked upon as about 12 days.

It was at one time thought that a certain minimum number of gametocytes had to be present in the blood before the mosquito would become infected, this number was placed at 12 by Darling (1909). Recent work has shown that there are many other factors besides the number of gametocytes that determine infection of the mosquito, these include species and strain of plasmodium, and species and individual variability of mosquito, some individuals of recognized vector species being entirely refractory to infection.

Development only takes place in the female mosquito

There is considerable uncertainty as to exactly what happens to the sporozoite when it enters man. A few facts are known: it does not, for example, remain in the blood stream, for blood taken during the first eight days is not infective. On analogy with observations made in birds it is thought that the parasite enters certain reticulo-endothelial cells of the host and there multiplies by schizogony. After this latent period the malaria parasite reappears in the peripheral blood as a ring form, it then completes a number of asexual cycles and may again become a gametocyte.

The term 'mosquito cycle' is sometimes used but actually there is no cycle in the mosquito. The parasites enter the mosquito as gametocytes and leave it as sporozoites. From a pair of gametocytes a very large number of sporozoites are formed.

transmitting malaria for over 90 days. The sexual cycle is only completed when gametocytes are again formed, thus both the mosquito and man are essential for this cycle to take place. The average period of the sexual cycle is at least a month, this is made up by about 12 days' development in the mosquito about 12 days' incubation period in man, and say another six days from the time the infection reaches the clinical 'threshold' to the appearance of gametocytes, these figures are not minimal but probably represent a low average.

The essentials for the natural transmission of malaria and the factors influencing them —

The essentials are —

- A *The malaria parasite*
- B *The mosquito vector*
- C *Man*
- D *The links between B and C, i.e. the lines of communication along which the parasite travels*

In the absence of any one of these essentials, malaria will not exist. If the conditions influencing all these four essentials favour malarogenesis the incidence of malaria will be maximal; if conditions influencing any of them are unfavourable malaria incidence will be sub maximal; and if conditions influencing all of them are unfavourable malaria will be minimal, or may not occur.

It is by the study of the various climatic and other terrestrial factors that influence these four essentials that we shall understand and explain the observed facts regarding the incidence, distribution etc., of malaria, which we have recorded and which we know as the epidemiology of the disease.

This is not however an academic study for it is only by knowing what these malarigenous factors are and how they exert their influence that we can hope to eliminate, reduce or avoid these influences. The study of how this has been and is being done, how it can be done and how it might be done constitute the science of malariology; even the essentials of which would fill a large volume here it is only possible to give the barest outline.

The malarogenic factors are conveniently grouped under these four headings —

**A The malaria parasite** —As a very large proportion of the human race has been or is infected with some species of malaria parasite, it is very unlikely that a community exists where the other three essentials are present and yet there are no malaria parasites, such a state of affairs is conceivable (and has a parallel in another disease, *i.e.* yellow fever), and, as long as no infected man or mosquito was introduced, the community would remain free from malaria

However, apart from these theoretical considerations the parasite factor is an important one, and malaria in any locality will be influenced largely by the number and immunological variety of the strains of malaria parasite present. Further it has been shown that other conditions remaining unchanged new strains of malaria parasite introduced into a community by immigration of foreigners importation of foreign labour, etc (*vide supra*), will cause a sharp rise in the incidence of malaria in that community

Again, the proximity of the reservoirs of malarial infection will be an important factor in determining the incidence in a locality

The parasite has two phases and the factors that influence it will be different in each case

In the development of the mosquito only takes place up to the oocyst stage. A temperature of 60°F and a humidity of 63 per cent (to ensure longevity of the mosquito) are necessary for the development of *P. falciparum*. This explains the absence of malignant tertian malaria from cold countries its autumn periodicity in temperate countries and in hot countries its disappearance during periods of very high temperature but low humidity

Other possibilities that have not yet been fully explored are the existence of other parasitic infections in the mosquito and the nature of its food, for mosquitoes take other fluids besides their blood meals

In man, the parasite is influenced by the host's natural and acquired immunity (*vide infra*)

Another factor is the formation of gametocytes. It has been suggested that this is a phenomenon of immunity but this is quite obviously not the case for infants who enjoy the least immunity are the greatest gametocyte producers. If therefore any correlation between gametocyte formation and immunity exists, it is a negative one

For transmission to occur there must be gametocytes in the peripheral blood, their presence, quantitatively considered, is therefore an important factor in malarogenesis

Finally, the effects of therapy have to be considered under this heading, any drug that destroys gametocytes directly or indirectly is capable of influencing malarial endemicity

**B The mosquito vector** —Not all mosquitoes carry malaria, only

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to the species. Similarly, the length of life of the adult mosquito varies considerably, in cold climates where it undergoes periods of hibernation, it will live up to nine months, but in the tropics, where metabolism is speeded

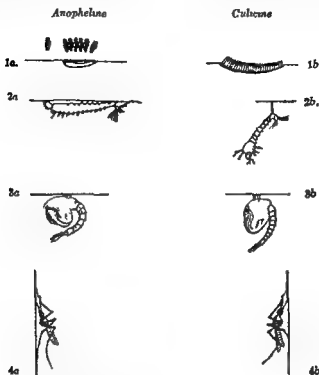


Figure 10

- | <i>Anopheles</i>                                  | <i>Culex</i>                               |
|---|--|
| 1a Eggs with floats also shows how they float     | 1b Eggs and float                          |
| 2a Larva floats horizontally on the water surface | 2b Larva hanging from water surface        |
| 3a Pupa breathing trumpets funnel-shaped          | 3b Pupa breathing trumpets long and narrow |
| 4a Imago body straight                            | 4b Imago hunch-backed                      |

up, its average life span is probably less than a month. In nature, the mosquito is subject to many adverse influences, infections, ecto-parasites, and innumerable natural enemies, fish in the water, bats in the air, and lizards on the wall, so, though it is extremely fertile, its life is a precarious one, this is an important factor and explains the relatively low sporozoite infection rate amongst mosquitoes caught in nature even in a highly malarious locality.

With this complicated life cycle it will be obvious that the factors that influence the mosquito will be numerous, these include temperature, humidity, rainfall, sub-soil water level, the nature of the water, the nature of the soil, physiographical conditions, both natural and man-

made, altitude (mainly in its relation to temperature), vegetation, biological competition, and natural enemies

When these conditions are very unfavourable mosquitoes will be reduced to a minimum, or they may be absent altogether and malaria will not occur, but there are places where the conditions are extremely favourable

increase in malaria

It is impossible to summarize the effects of these various factors, or to make any dogmatic statements, such as, for example, that rainfall is favourable to mosquitoes, for it may be just the reverse, and there are many circumstances in which rainfall will actually stop malarial incidence, or that abundant vegetation favours the mosquito and malarial incidence, for there are some vector species that disappear when streams are shaded (*Anopheles minimus*), though others (*A. umbrosus*) require shade, some mosquitoes flourish only in clear water, others are less particular and seem to prefer contaminated water, yet others need a degree of salinity (*A. sudaicus*), some prefer stagnant pools, others running water, and so on. It does not mean that, because this information cannot be summarized, our knowledge on these subjects is confused and unsatisfactory. On the contrary, there is a very great deal of accurate and detailed information on the habits of most of the important vector species. It is a matter of primary importance that anyone who has any responsibility in the matter of malaria control should find out first what are the local vector species and the relative importance of each, he should then ascertain from the numerous books and other publications on malariology what are the habits of these species and finally by observation he should find out how they behave in relation to their normal behaviour. There are many species behaving differently in different parts of the world. For example, *Anopheles gambiae* feeds exclusively on man in the Wynaad and Malabar regions, a potent vector, whereas in the Himalayan foot-hills it feeds exclusively on cattle and is of practically no importance as a vector, but such instances are rare, and the instances in which in nature they have been made to change their habits (e.g. to breed in fresh water when they have been deprived of saline water) are even rarer. It will usually be found that one species only is of real importance and this will facilitate control very considerably.

C Man.—The influence of the human factor in the determination of malarial incidence has been to some extent neglected since the day when attention was first attracted to the parasite and the mosquito.

For all practical purposes, man is the only intermediate host of the malaria species with which we are now concerned, though in certain jungle areas a higher mosquito-infection rate than appears to be explainable on the grounds of the very sparse human population has led to the suggestion that apes may be the source of infection. There are of course many other plasmodia besides the four 'human' species, and man has been infected with the monkey plasmodium, *P. knowlesi*, under artificial conditions.

The important factors under this heading are the density and age composition of the population, the previous malarial experience of the community as a whole or of the different groups that compose a community, the climatic conditions under which they live, their economic status and general mode of life, and their general state of health and nutrition.

Man enjoys both natural and acquired immunity to malarial infection

man with malaria and there are the many instances when the malaria has not developed for some years, until the host has been subjected to cold or some physical strain and his natural resistance thereby lowered

There is as yet no agreement on the nature of acquired immunity. There is little doubt that some, both cellular and humoral, immunity is acquired and that to a certain degree it is specific and to a much less

The other explanations from malaria is that all were killed off in their infancy, or that the apparent immunity is really a 'premunition', that is to say, the individual is already infected with malaria so that his body defences are active and prevent super-infection, which some might argue, constitutes immunity

high infection rate, though short of 100 per cent but the average number of parasites will be far less, amounting to perhaps one-hundredth that in the infants, and they will only suffer from occasional febrile attacks. Christophers (1925) has shown that, under these conditions, the infection rate, the parasite count and the frequency of the febrile attacks show a steady decline as the age advances

There is however no doubt that this immunity is very labile and that when the general powers of resistance of the host are lowered for any reason, for example, by famine and hardships, as well as by fatigue and cold, mentioned above, he is far more susceptible to malarial morbidity, even if not to malarial infection

Conversely, when they are raised by good food and comfortable living conditions, he will be much less liable to malarial morbidity and probably to malarial infection

Thus, immunity is important to the individual, but even more important to the community, for the rise in immunity means a reduction in the circulating parasites and therefore in the source of infection to others. Conversely, a bad general breakdown in immunity, from any cause, will lead to a vicious circle of increased infection and increased morbidity, sudden disastrous epidemics that sometimes occur even in endemic areas are explainable in this way

The presence of children in a community will increase incidence both on account of the heavy infections that they suffer as a result of their low immunity, and because they produce large numbers of gametocytes

The introduction of a number of non immunes—either non immune to all malaria strains or to the local strains—into a malarious community will be like adding fuel to a smouldering fire, and will increase malaria incidence in the whole community

**D The links between man and the mosquito**—Both man and the mosquito are essential but if they could be kept apart malaria would die out. The stronger the links, the higher the malaria incidence, and vice versa. The important factors can be considered under two headings, (i) general and (ii) local and personal

(i) The general factors include density of human population, density of mosquito vector population, living conditions of the population, and movements of the population, air movements and prevailing winds, and animal deviation (zoophilism)

This question of the densities of the human and mosquito populations and malaria incidence is a mathematical problem, but it is not an entirely simple one. On the whole the denser the populations the greater are the chances of contact between man and the mosquito, but this would seem to suggest that the disease should be more prevalent in towns, whereas we know that it is not. The reason for this is that in towns the density of the human population is more than counterbalanced by the sparsity of the mosquito population

Again it must be remembered that to transmit malaria the mosquito must take at least two human blood feeds, there are many factors which militate against the chance of this occurring for example, the high mortality amongst mosquitoes in nature, which means a short survival period for each individual mosquito this cannot be entirely compensated by a higher propagation rate which would only mean that a larger number of mosquitoes took a single blood meal. Here also the effect of wind will be felt, mosquitoes, which are very capable of flight against the human blood meals

The chance of contact between man and mosquito will also vary considerably with differences in the living conditions. If the people are poor and live in dark ill-ventilated huts, in the corners of the huts during almost uninterrupted on their hunches of transmission will be great. If the people are well-to-do and live in well-lighted and well-ventilated houses

light, they will have to leave the house, have to be obviously not return, 1 of the once-fed mosquitoes and the chances of a second feed being taken are considerably reduced. If in addition protective measures are used by the people, the chances are reduced still further, but this is a personal matter and will be considered below

Zoophilism or animal deviation is undoubtedly an important factor although there are different schools of thought on this subject. The original view expressed by Roubaud was that the proximity of cattle deflected mosquitoes from their human hosts, but the evidence on this subject has been confusing and it is obvious that in some circumstances cattle attract mosquitoes to their vicinity and thereby favour malaria transmission amongst the people living in close association with them. The fact that some species that are known as potential vectors and yet are



of enlargement is a good indication of the extent of the parasitic infection, whereas others claim that the reverse is usually the case. The writer takes the view that splenic enlargement is evidence of imperfect host-parasite adjustment. In hyper-endemic areas, immunity in the child is low, parasitic infections are heavy and considerable splenic enlargement is the rule. In the well-nourished adult, immunity is high, parasitic infections though common are light, and the spleen is small. Finally, in the ill-nourished adult of the poorer malarious districts, immunity is again low, and parasitic infection is kept down only by the continuous parasite—and incidentally red-cell—destruction by the hypertrophied reticulo-endothelial tissues, so that splenic enlargement and anæmia characterize the clinical picture.

**Macroscopically**, in very acute cases, the spleen is moderately enlarged, dark red and congested, the capsule which under pressure retracts when it is cut and a dark red substance oozes out. In less acute cases, it is moderately enlarged, firm and slate coloured, when cut, the capsule does not contract in the same way, but a certain amount of black tarry substance is seen on the slate-coloured cut surface. In chronic cases, the capsule is thickened and shows the organ may weigh anything up to 10 pounds, but it is firm, not very dark, and shows white fibrous trabeculae.

**Microscopically**, there is a general hyperplasia in which both elements take part, later, there is an issue at the expense of the malpighian cells are loaded with red-cell and parasite debris and hæmoglobin pigment, but, in chronic malaria, parasites may be absent and pigment very scanty.

**Other organs**—The liver is enlarged, the gall-bladder is distended, and on section the liver may show a dark red surface, but in certain cases in which there has been very excessive hæmolysis (e.g. blackwater fever) there will be a distinct yellowish colour, the result of hæmosiderin staining, in addition to the dark brown of the specific hæmoglobin pigment. The organ gives a marked prussian-blue reaction with potassium ferrocyanide. Under the microscope the Kupffer's cells are seen loaded with pigment and debris and the bile canaliculi are dilated, in more chronic cases there are degenerative changes in the parenchyma cells.

The active bone marrow is dark red, but the hyperplasia is mainly confined to the phagocytic reticulo-endothelial cells, which contain pigment and debris, to the detriment of the specialized hæmopoietic tissue. Parasites are usually present in fair numbers, but, from biopsy experience, there is no reason to believe that there is any particular aggregation of parasites in this site.

In fatal malignant tertian infections with cerebral symptoms, there

forming a granulomatous area around an arteriole usually in the cortex. The blocking of the arterioles is caused by a chemico physical change in the blood elements, an increase in stickiness of the parasitized red cells resulting from fibrin deposition which causes them to aggregate in large masses, and a local hæmo concentration due to plasma filtration into the tissues. This blocking of the arterioles is seen best in a smear made by crushing a small piece of brain cortex between two slides and staining them by Giemsa's method.

## THE BLOOD

The kidneys are involved in acute cases but do not as a rule show any characteristic changes there are however cases of acute and sub-acute nephritis of undoubted malarial origin, and the rarity of this complication suggests that it may be an allergic phenomenon due to sensitization by the foreign proteins from parasite and tissue destruction in a previous attack. The kidney changes in the sub-acute attack are of the glomerulo-tubular nephrotic type. In blackwater fever (q.v.) there are characteristic changes.

There may be blocking of the arterioles in other organs and tissues of the body e.g. the pancreas and intestinal mucosa, these cause the process localized manifestations of malaria such as malarial dysentery and a condition simulating acute pancreatitis.

The degenerative changes attributed to the malarial 'toxin' that occur in many organs are too indefinite to discuss in detail it is very often doubtful if the changes noted are really due to the malaria or to some toxic condition.

**The blood.**—There is nearly always some anaemia the degree will depend on the duration of the attack and on other circumstances but it is disproportionate to the number of the red cells that have actually been destroyed by malarial parasites and in the acute infection there is evidence of depression of haemopoietic function of the bone-marrow. There is additional indirect evidence for this the deduction is made from the fact that before treatment is given though there is anaemia there is at first no rise in the percentage of reticulocytes but that about six to eight days after specific treatment has been instituted there is a sharp rise in reticulocytes (evidence of sudden active regeneration of red cells) suggesting that some depressing influence has been lifted. These studies have been made most in Great Britain and in primary induced malaria we have not been able to confirm them in malaria in an endemic area. On the other hand have found that the bilirubinæmia is very frequently not as high as would have expected had the anaemia been solely the result of red destruction that is to say had it been a hæmolytic anaemia.

The anaemia is usually normocytic.

There is a slight fall in leucocytes which starts just before the attack the leucopenia is maintained throughout the attack and some for some days after the temperature has returned to normal (see figure 11). The def.

for some days after the temperature has returned to normal (see figure 11). The def.

usually about 5,000 leucocytes per c.mm. (see figure 11). The def.

is mainly in the granulocytes and there is usually an actual as well as a relative increase in large mononuclear.

In the absence of kala-azar and certain rarer blood diseases a large mononuclear count of 10 per cent or over is said to be diagnostic of present or past malaria.

The van den Bergh indirect reaction may be slightly increased during an acute attack, but it is not constantly so.

The blood sugar is reduced.

The erythrocyte sedimentation rate is much increased whilst the infection persists.

(The specific findings: malarial parasites, pigment and Schuffner's and Maurer's dots are discussed under the heading of diagnosis.)

Days before  
first  
attack  
parasite



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**The urine**—During the febrile attack, the urine is usually concentrated and exhibits the ordinary 'febrile' characteristics

Urea excretion is increased and the chlorides and phosphates are often diminished

Urobilin is increased considerably during the attack. There is quite frequently a trace of albumin at the onset, and in some cases of both quartan and malignant tertian malaria—traditionally in the former, but in the writer's experience just as frequently in the latter—a heavy cloud of albumin and granular and hyaline casts

Quinine albuminuria was not uncommon when large doses of quinine were the rule, but, with a maximum of 30 grains a day, this seldom occurs

**Wassermann** . . . . .  
undoubtedly  
Webb and K. . . . .  
and both tests in 23, of 25 induced malarias. From his experience with naturally acquired malaria, the writer is convinced that this so-called 'false-positive' Wassermann reaction frequently occurs in this disease, it is usually transitory but may persist for some weeks. It is however certainly not as constant a finding as the experience with induced malaria, quoted above, would suggest

### SYMPTOMATOLOGY

**Introduction**—The clinical manifestations of malaria are so protean that it

**Incubation period**—The first symptoms do not appear until the malaria infection has reached a certain critical level, this is usually given as about 100 million parasites

The variations in the incubation period in different species are explained by simple arithmetic. Let us take the cases of malignant tertian and quartan, and suppose the human host was allowed to multiply; they will serve our purpose. The average rosette contains 24 merozoite. In the tertian, shed by 24 every 48 hours and the 100 million mark will be passed in 12 days, whereas in quartan, with an average of 10 merozoites per rosette which matures every 72 hours, it would take 24 days to reach the critical figure of 100 million parasites. Many merozoites of course fail to reach a red cell and are destroyed, and there are other factors which put a brake on reproduction, but it is easy to see why malignant tertian with its maximum production of 32 merozoites may have a very short incubation period and why quartan with its low merozoite production and 72-hour cycle is likely to have the longest

The incubation period of benign tertian is usually about 14 days, in malignant tertian it may be as short as eight days and is usually less than

**Prodromal symptoms** before the actual onset are not uncommon, lassitude, anorexia, headache and a slight sense of chilliness, if the

temperature were taken, a low pyrexia,  $99^{\circ}\text{F}$  or so would probably be found. In cases under close observation, a daily, or a 48 hourly, rise up to  $99^{\circ}\text{F}$  is the rule, these small rises in temperature correspond with the bursting of successive crops of rosettes before the infection has quite reached the true clinical threshold.

The true onset is sudden, there are three stages in the attack —

**The rigor** — There is a feeling of extreme coldness, the patient shivers from head to foot sometimes shaking the whole bed, the teeth chatter, he pulls over himself all the blankets he can reach but it makes no difference to his feeling of coldness, the skin feels dry and the condition known as goose flesh is common, the features become pinched and he has the blue appearance of a cold person. All this time the temperature is rising and after about an hour the shivering gradually ceases and the patient passes into the next stage.

be prolonged

**The sweating stage** — The patient suddenly bursts into a profuse perspiration, the sweat pours from him. A feeling of great relief comes over the patient and all the symptoms of the previous stage disappear. The temperature falls and may be sub normal. He now feels 'washed out' and tired and will usually go to sleep. When he wakes up he feels perfectly well and is often prepared to get up and go about his ordinary daily routine.

The whole attack occupies six to ten hours. The rigor coincides with the bursting of the rosettes. When a rosette bursts, there is a sudden release into the blood stream of not only the merozoites but of red-cell debris and probably certain products of malaria parasite metabolism. The rigor is an anaphylactic phenomenon sensitivity having been worked up by the bursting of the earlier crops of rosettes. Manson-Bahr states that the attack usually occurs in the morning, but this is not the experience of the writer, it may occur at any time.

**The periodicity of the malarial attack** — This is dependent on the plasmodial cycle so that in tertian malaria it will occur every 48 hours and

burst on the even days of the month and the other crop on the odd days, so that the patient will have a rigor daily (Hippocrates' quotidian malaria), or, if the infection is quartan, on two days out of three

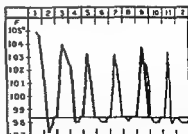


Figure 12 Benign tertian malaria

In the initial attack of benign tertian malaria in a non immune the onset may be with a typical rigor, but much more frequently there is a daily



Benign tertian malaria shows a far greater tendency to relapse after treatment than malignant tertian. Figure 15 shows the times when relapses usually occur. In benign tertian malaria, the late relapse, the peak of which occurs at about the 28th week, probably accounts for the spring rise in malarial incidence that has been reported in some countries where the temperature precludes transmission at this time of year.

Other specific clinical characteristics—It is by no means always possible to distinguish between the four different malaria infections clinically, except where quartan periodicity is clear, but the different infections have their special characteristics.

In malignant tertian the temperature chart much less frequently follows the classical form. It is usually remittent and not intermittent, and quite often the temperature is maintained at a high level for 36 hours only falling a few hours

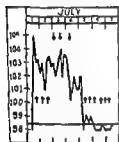


Figure 10 Malignant tertian malaria showing sustained rise despite treatment. Oral administration failed to control fever, thus necessitated three intravenous injections.

↑ = oral quinine  
↓ = intravenous quinine

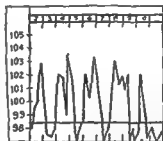


Figure 17 Malignant tertian malaria showing tertian periodicity

and, though spontaneous remissions obviously do occur (or the mortality would be much higher than it is), the danger of cerebral symptoms supervening precludes experiments in patients under observation to ascertain how soon remission will occur. Relapses after adequate treatment are not common but when they do occur

are likely to be as serious as the initial attack.

Figure 1B shows that, if a relapse is going to occur, it will usually occur within the first few weeks.

Quartan malaria is usually no more severe than benign tertian, splenic enlargement is less marked, but nephritis is said to be much more common, in some places it has been reported in 40 per cent of the cases, the albumin in the urine showing an increase with each attack.

Malaria due to *Plasmodium ovale* is very mild shows a marked tendency to early spontaneous remission, and responds rapidly to treatment

In an endemic area where more than one species of parasite occurs mixed infections are very common. In Calcutta, where many cases of malaria are seen, it sometimes takes us many weeks to find what appears to be a pure benign tertian infection, even then, though many films have been searched and only benign tertian parasite found, this blood injected into another man, for purposes of malaria therapy.

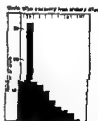


Figure 18. Time of relapse of 63 cases of malignant teratoma

will often give rise to a mixed infection, with the dangerous malignant tertian predominating

**Other signs and symptoms of the ordinary attack**—The spleen enlarges during an attack and subsides between attacks, but this frequent enlargement leads to hypertrophy and it tends to become larger at each successive attack. The spleen may not be palpable during the first few febrile attacks of a primary infection, but in re-infections or relapses it provides a valuable indication of the nature of the fever. The spleen has been known to rupture spontaneously during a malarial attack, there is a sudden severe pain in the abdomen, but this is quite often not in the splenic area (see also Diagnosis)

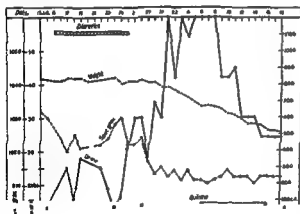
liver  
this  
hepatitis

and congestion of the  
very frequent symptom,  
confusion with amoebic

A feeling of pressure in the thighs and legs, and sometimes actual pain in the legs are symptoms well recognized by patients subjected to frequent malarial attacks

pleocholia, followed by  
An icteric tinge of the  
al in severe malignant  
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aria by no means rare

Acute  
infection  
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In infants the temperature will seldom run the usual course, it is nearly always a high remittent or even continuous fever, but shows great irregularity. Vomiting occurs early and is frequent. The spleen enlarges rapidly and usually the liver also. Convulsions replace the rigor that occurs in an adult. Very prompt vigorous treatment is necessary, as early death

due to hyperpyrexia and cerebral involvement is common, but a comatose child will often come round completely in a few hours

In pregnant women malaria if left untreated will be fatal to the child and dangerous to the woman. Still-birth and abortion are very common, these are sometimes said to be due to the blocking of the placental vessels with subsequent separation of the placenta. This is not the mechanism, since the parasites do not normally reach the placental circulation. The

parasites seem to have a particular affinity for the decidual blood vessels, the placenta after parturition will be a case in which few were to be seen.

The decidual vessels are, however, too large to allow blocking by malaria parasites, and the abortion is more likely to be the result of some toxic effect. Malarial subjects are more liable to the toxæmias and to the severe macrocytic anæmia of pregnancy. It is imperative therefore that treatment should be undertaken immediately malaria is diagnosed in a pregnant woman.

### SPECIAL CLINICAL TYPES OF MALARIA

**A Pernicious**—This is usually associated with malignant tertian infection, but sometimes with quartan and even benign tertian. The different forms that pernicious malaria may take are almost unlimited, but those most frequently encountered can be grouped as follows—

- (i) **Cerebral forms**—(a) The heat centre may be affected, the

febrile symptoms

The other symptoms associated with the cerebral type are a full bounding and rapid pulse, a flushed face, sighing respirations, and vomiting.

In these cases the differential diagnosis from heat stroke, apoplexy, epilepsy, diabetic coma, meningitis, alcoholism, and trauma may be difficult.

- (ii) **Algid forms**—There may be sudden collapse with no other symptoms or this collapse may be associated with hæmorrhagic vomiting, cramps and suppression of urine, mucus in the stools, or with other signs for example, hæmorrhagic

The characteristic symptoms in the algid form are collapse, a weak thready pulse, sometimes barely perceptible, a cold clammy skin, a weak voice, and slow shallow respirations. The patient may recover fairly rapidly or may pass on into a 'typhoid state' for some days. The localizing symptoms are due to the blocking of the arterioles by malaria parasites in the particular locality, as occurs in the brain in the cerebral forms.

- (iii) **Bilious remittent fever**—This is a form of severe malignant tertian malaria that was distinguished clinically from the ordinary malarial attack in the days before the parasite was discovered. It seems less

severe, this will increase

It is distinguished from its early appearance and conditions jaundice does in particular, it increases

steadily

(iv) *Blackwater fever* — [This will be considered separately]

(v) Other types that do not fall into any of the above groups are the cardiac and the broncho-pneumonic. They are self-explanatory.

**B Chronic malaria** — This term is falling into disfavour with the malarialogist, probably rightly so, because its exact meaning is not clearly defined. There is, first, the chronic relapsing malaria that is usually simply malaria that has been inadequately treated. Even after a full course of cinchona, the relapse rate in benign tertian is high and the treatment may have to be repeated for two, three, or even more relapses, but eventually it will respond. It is surprising how many people there are, including doctors, who after a single infection will allow themselves to suffer for years for want of adequate treatment.

In the next group are those persons who are subjected to repeated infection for years, often three or four times a year, which are not necessarily those that are infected seasonally, and those that are infected perennially. This subject has not been sufficiently studied and the different reactions of the individual to these repeated infections are found in the to suffer very spleens, which tion, and they 1) There are others who suffer periodic attacks of fever, are weak, debilitated, and anæmic, have enlarged spleens, are very subject to other infections, and are altogether of poor value to the community, on proper treatment, these patients will recover completely and again become really useful members of society.

Finally, there is the chronic malarial cachexia. The patient has a huge spleen and liver, œdema and often ascites, he is very anæmic, has an earthy complexion and often some jaundice, he may or may not have low fever of endogenous origin, not being due to malaria but to other infections, such as kala azar or bilharziasis, but this sequel, as perhaps it should be called to malaria is undoubtedly very common in many endemic areas, though parasites are not often present and the patient does not respond well to anti-malaria treatment.

What determines the different reactions to malaria infection in

ryot on a very poor diet with a low protein intake, the different stages of chronic malarial morbidity up to the stage of malarial cachexia.

**C Latent malaria** — This is an interesting and sometimes important phenomenon of malaria infection. It may be commoner than we imagine, but it can only be demonstrated properly in a person who leaves the place where he has been infected and lives in a malaria-free country. It is not uncommon in people returning home from the tropics when they are subjected to the rigours of an English winter; other physical strains, such

to give a course of cinchona as a routine measure before the confinement of or a surgical operation on anyone coming from a highly malarious area

### DIAGNOSIS

The diagnosis should be considered under five headings—the history the fever the spleen the blood film and response to therapy

**A The history**—Before making a diagnosis of malaria one should be satisfied that the patient at some time even if not recently has been in a malarious country. Latent malaria will seldom if ever make its first appearance more than a year after infection the last possible chance that the patient had of being infected should be carefully ascertained

in the tropics without having a single attack of malaria

A history of a previous attack is also suggestive but here again it is necessary to be cautious because to the layman in the tropics fever is synonymous with malaria and the patient should be questioned as to whether a diagnosis was made on a blood examination whether the typical rigor and malarial periodicity were exhibited and whether there was response to cinchona (or mepacrine). Undue weight should not be given to the answer to the last question

**B The fever**—The classical fever charts of tertian and quartan

and is not usually maintained for any length of time

On the other hand malaria must not be excluded just because the temperature chart does not conform to any of the classical types and rigors are absent the chart may take almost any form in uncomplicated malaria and malaria may be complicating any other disease

**C The spleen**—There are many other diseases in the tropics that are important to know if the spleen is enlarged. Rapid enlargement of the spleen is seen in malarial attack and intermission. The spleen is slightly tender in malarial attack and in the spleen of typhoid. In chronic malaria as the spleen enlarges it becomes firmer and eventually assumes a wood like hardness as a result of the fibrotic changes that have taken place in these stages it is not tender

In tropical practice unless the spleen is palpable with the patient lying on his back with his legs drawn up or standing and bending forward slightly



the enlargement is not usually of much importance, the apparently painful contortions sometimes depicted in textbooks are not to be recommended

**D The blood film**—The examination of the blood film is the most important procedure in the diagnosis of malaria

Even one or two doses of cinchona or other anti-malarial drug will make the finding of parasites very difficult, so that the blood should be taken (but not necessarily examined) before any such drug is given

Whilst one would not recommend postponing the taking of the blood film, it should be remembered that immediately after a rigor, though the parasites will be most numerous, the large majority will be very young, and therefore very small, rings, these are not as easy to find as the larger trophozoites of some hours later. (It is on this principle that the so-called

no actual multiplication takes place ;

**Methods of examining the peripheral blood**—The blood can be examined by the thin film, the thick film, and the so-called cultural methods. The last-named is a refinement investigation is being carried ( 'culture' cannot be accepted parasites. It is not a method cedure, and it need not be described here

The Romanowsky-stained thin film is the method most frequently used, but the thick-film method is gaining popularity as the technique of of the thick-film method is that a much med and a scanty infection, especially of The disadvantages are that the number so accurately, that the parasites them- cannot be s their ed cell it seen made species may rem such as size, sta so readily. For

parasites are found in the latter and their identity is uncertain, a return to the thin film can be made and this re-examined with more confidence. It is much easier to find parasites when you know they are there, than when you just think they may be there

the thick film for the

the exact number of parasites, this is easily and accurately done by ing with the blood an equal quantity of fowl's blood-corpuscle suspension of known concentration

A thin blood film is then made from the mixture, this is stained and field by field the number of fowl's red corpuscles (easily distinguished by their oval shape and nuclei) on the one hand and malaria parasites on the other are counted

The ratio of one to the other is worked out and as the number of fowl corpuscles per mm is already known, the number of malaria parasites can be calculated.

Finally, the giving of adrenaline to cause a contraction of the spleen, so that parasitized red cells in the spleen sinuses are forced into the circulation, is a method worth employing in hospital cases, when parasites cannot be found by any of the above methods. Either 0.5 c cm of 1 in 1,000 adrenaline should be given subcutaneously, 20 minutes before, or 0.01 c cm intravenously, five minutes before the blood is taken, the latter will be more effective.

**Technique**—The first essential in making a good thin film is to have perfectly clean slides and a good spreader. The coverslip of a haemocytometer makes an almost ideal spreader. Otherwise one should select a good thick microscopic slide with a good edge and cut off the two corners\* to make the spreading edge slightly narrower than the slide on which the film is to be spread.

The blood can be taken from the lobe of the ear or the finger. The part should be previously sterilized with alcohol and ether but it must be allowed to dry completely or be rubbed with dry sterile cotton wool. The needle, which must be similarly sterilized, must be similarly dried. The drop of blood is then placed on the slide and the spreader is used to spread the drop.

the slide (figure 20)

proof slide box for staining at a later date. The unstained slides must never be left uncovered on the working table as blood is readily eaten by flies during the day and by cockroaches at night.

Romanowsky stains especially those as modified by Leishman, Wright, Jenner and Giemsa are the most satisfactory. All these stains depend for their action on the compounds formed by the interaction of methylene blue and eosin and the differences between the various stains are dependent on the proportion of the two dyes. The fluid stains except Giemsa's stain are prepared by dissolving the dry powder in acetone free pure methyl alcohol so that a preliminary fixation with methyl alcohol is only required in the case of Giemsa's stain. Leishman's and Wright's stains are used in the strength of 0.15 per cent and Jenner's stain in the strength of 0.5 per cent.

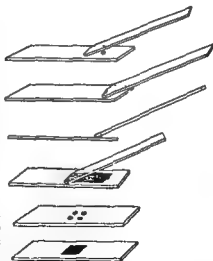


Figure 20 Methods of making thin and thick films

\*This can be done by making a scratch across each corner with a glass cutter or very simply by holding the slides under water in a basin and cutting off the corners with an ordinary pair of scissors.

**Preparing Leishman's or Wright's stain.**—Stains in powder or tablet forms and extra-pure acetone-free methyl alcohol for dissolving them should be obtained from some reliable firm. We have found the Gurr's\* stains to be very satisfactory.

All the glassware used in preparing the stains and in storing them should be scrupulously clean and free from any trace of water, they should be rinsed first with absolute alcohol and finally with a little methyl alcohol.

**Staining with Leishman's or Wright's stain.**—Put the slides on a staining rack taking care that the side with the blood film is upwards, also see that the two ends of the slides are in the same plane.

From a drop bottle, or with a pipette, pour on sufficient stain to cover the whole of the film, wait for one minute to allow for proper fixing, with a capillary pipette now add two to three parts of distilled water (pH 6.8 to 7.0) or the buffer solution†. With another capillary pipette or glass rod thoroughly mix the stain with the diluent to ensure of uniform mixture over the film.

When the mixture is allowed to settle, a scum will form on the top, if the proportion of the stain and diluent is correct. Allow the diluted stain to act for 5 to 10 minutes.

The diluted or undiluted stains on the slides must not be allowed to dry up at any stage of the staining. Drying is prevented by covering the staining rack with a wide bell-jar, or other improvised device, this is a very necessary precaution in hot dry climates.

When the staining is complete, wash off the excess stain with a generous amount of the buffer solution. Tap water may be as satisfactory, but this varies from place to place so that its suitability must first be tested. This will wash off all the stain.

When it is dry the slide is ready to be examined.

**Staining with Giemsa's stain.**—It is more difficult to prepare this stain and it is better to purchase it in solution. Giemsa's stain as prepared by Gurr is very satisfactory.

For staining with Giemsa's stain, preliminary fixing with methyl alcohol or some other fixative is absolutely necessary.

The optimum appearance of Giemsa-stained slides can only be learned by experience, but it is best described as a rich purple.

**Preparing dilute solution.**—Take about 20 c.cm of prepared distilled water (pH 7.0) or buffer solution in a clean transparent glass cylinder, add 20 drops of undiluted stain or in other words as many drops of stain as there are cubic centimetres of water. Mix well by inverting the cylinder and see that the depth of colour of the mixture is such that, when held in front of the eyes, it allows a distant object to be seen through it.

\* George T. Gurr, 136 New Kings Road, London, S.W.6, England.

† Monopotassium phosphate—6.63 gm.

Anhydrous disodium hydrogen phosphate—2.56 gm (or 6.46 gm of  $\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$ )

Distilled water up to 1 litre

Add 1 c.cm of chloroform as preservative

he slide with methyl  
do s not dry up on  
minutes remove the

Now flood the slide with the diluted stain cover with a bell jar and allow the stain to act for at least half an hour or better still leave it overnight. Next morning wash and dry the slide as suggested above.

The film is then

**Staining**—Two methods of staining the thick film are described. The former

**Method I.**—The film should be allowed to dry for two hours at room temperature or in a bacteriological incubator (37 C) for one hour.

Dehæmoglobinize the film with the following solution —

2.5 per cent solution glacial acetic acid	4 parts
20 per cent solution crystalline tartaric acid	1 part

This mixture keeps indefinitely it should be kept in a glass-stoppered bottle.

Lay the film on the staining rack and gently flood it with the mixture. This process should be watched as thick patches will take longer than the rest to dehæmoglobinize. Complete dehæmoglobinization is indicated by the whole film becoming greyish white.

As soon as dehæmoglobinization is complete drain off the fluid by gently tilting the slide. Flood the slide with methyl alcohol and allow this to remain for five minutes. The film is now dehæmoglobinized and fixed.

Drain off the methyl alcohol and wash the film very thoroughly with neutral or very slightly alkaline distilled water. Every trace of acid must be removed.

Stain the film with dilute Gens's stain one drop to each cubic centimetre of distilled water for 20 minutes or longer. Wash in distilled water. Do not blot the film but let it dry by slanting it against a vertical surface film side inwards.

**Method II.**—For this method two solutions are required —

#### **Solution A**

Methylene blue	0.8 gm
Azure I	0.5
Disodium hydrogen phosphate (anhydrous)	5 "
Potassium dihydrogen phosphate (anhydrous)	6.25 "
Distilled water	500 ccm

#### **Solution B**

Eosin	1 gm
Disodium hydrogen phosphate (anhydrous)	5
Potassium dihydrogen phosphate (anhydrous)	6.25
Distilled water	500 ccm

**Preparation of solutions.**—The phosphate salts are first dissolved then the stain is added. Solution of the granular azure I is aided by grinding in a mortar with a small quantity of the phosphate solvent. The solutions of the stain should be set aside for two hours when after filtration they are ready for use. Should a scum later appear on the surface or the dye precipitate on the stained films subsequent filtration is necessary.

The stains are kept in covered jars of such a size that the depth of the solution is about 3 inches, the level being maintained by the addition of fresh stain as necessary. Eosin solution should be discarded if it becomes greenish.



*P. falciparum* unless there are at least 32 merozoites)

The peripheral blood. The most characteristic (*P. falciparum*) The crescent is much longer than the diameter of a red corpuscle, so that it appears to extend beyond the red corpuscle, the pale outline of which is to be seen in the concavity of the crescent. The female is a long slender crescent, stains a dark blue, and has a compact nucleus around which the pigment is aggregated. The male gametocyte is stouter and less characteristically crescentic, with a large nucleus the pigment scattered, and the cytoplasm staining a pale blue.

The gametocytes of *P. vivax* are not so frequently encountered in the peripheral blood, they are round or ovoid and fill the corpuscle, the chromatin is aggregated into one mass, the pigment is scattered, and if there are any visible remains of the red corpuscle Schüffner's dots will be seen. The gametocyte of *P. malariae* is usually much smaller than that of *P. vivax*, but otherwise very similar. As in the case of *P. falciparum*, the nucleus in the female is more compact, and the staining of the cytoplasm darker.

The changes in the containing red corpuscles that occur are characteristic. In benign tertian infection (*P. vivax*), the cell is pale and considerably enlarged, and it exhibits regular fine eosinophil stippling throughout. The red corpuscle that contains the very young ring forms of *P. falciparum* is not enlarged and in fact may appear to be smaller than normal, but is really more globular. When the trophozoite enlarges, however, the cell also enlarges slightly, becomes slightly darker, and shows numerous Maurer's dots, or clefts, these are red or purplish, coarser, and much more irregular than Schüffner's dots. The red corpuscle in quartan (*P. malariae*) infection is similarly more globular but does not show Maurer's dots.

The pigment in benign tertian is a fine and lightish brown, in malignant tertian it is coarser, black, and forms clumps, and in quartan, it appears early, is very prominent, and falls between the other two in the matter of colour and coarseness.

*P. ovale* has not been included in this description up to the present, as it is a comparatively rare plasmodium. It is very similar to *P. vivax*, except that it is not amoeboid and the rosette contains 8 to 12 large merozoites, the red corpuscle which is only slightly enlarged shows more marked stippling than in *P. vivax*, but is of a slightly paler red. The special characteristic of the red cell in this case is the frequency with which it assumes an ovoid shape—it is from this and not from the shape of the parasite that its name is derived—or shows a fimbriated edge. (This fimbriation must occur during spreading and is an indication of some characteristic physical change within the cell rather than of any changes in shape that occur *in vivo*.)

TABLE I  
Identification of species of malaria parasites

Parasite	Changes in red cells	Pigment	Trophozoites	Adult schizonts	Merozoites	Gametocytes
BENIGN TERTIAN ( <i>Plasmodium vivax</i> ) 48-hour cycle	Large and pale with fine red stippling (Schüffner's dots)	Fine yellowish-brown granules or rods	Rings $\frac{1}{2}$ diameter of red cell growing forms very irregular with pale blue staining and indistinct outline Vacuole present	Completely fills red cell Irregular in shape	Medium size, 14-24 in number	i or ovoid larger than ii i deep blue staining as in and small compact plasma stains more blue or reddish with paler nucleus
QUARTAN ( <i>Plasmodium malariae</i> ) 72 hour cycle	Not enlarged No stippling	Coarse dark brown or almost black Appears early	Rings $\frac{1}{2}$ - $\frac{1}{3}$ diameter of red cell growing forms often band like or angular Cytoplasm dense early pigment	Fills red cell Daisy head rosette	Large size, 8-10 in number	i or ovoid the size of cell ii deep blue with small compact nucleus iii pale blue or pink iv large pale nucleus
MALIGNANT TERTIAN ( <i>Plasmodium falciparum</i> ) 48 hour cycle	Not enlarged spherical and show coarse stippling (Maurer's dots)	Blacker than in other forms clumps early	Young forms are fine hair-like rings about $\frac{1}{2}$ diameter of red cell with 2 chromatin dots and accolé forms common Larger rings are also seen Growing forms very rarely seen	Extremely rare in peripheral blood as they tend to adhere to blood vessel wall	Very small Number variable 8-32 or more	entic staining deep with a compact central mass with pigment ii ring-shaped staining blue with larger and nucleus and scattered
<i>Plasmodium vivax</i> 48 hour cycle	Very slightly enlarged paler than normal Stippling like P. vivax but coarser Ovoid or distorted fimbriated cells	Coarser than in P. vivax Dark yellowish brown	Rings about $\frac{1}{2}$ diameter of red cell not ameboid cytoplasm dense well defined chromatin large may be irregular	Mature forms slightly smaller than red cell daisy head rosette	Large size 8-12 in number chromatin sometimes crescentic	iii malinger iv red cells

To summarize, identification of the species depends on (i) changes in the red corpuscles, (ii) the nature of the pigment, (iii) the character of the trophozoites, (iv) the presence of the mature schizont—for they do not appear in the peripheral blood in malignant tertian (*P. falciparum*) infection—and their character, particularly with reference to the number of merozoites in the rosette, and (v) the character of the gametocytes. The data are summarized in table I which is a modification of the table given by Covell (1939)

Significance of the findings.—The finding of a malaria parasite naturally indicates that the patient has a malaria infection, but it does not necessarily mean that all his symptoms are due to malaria, for he may have some other disease and malaria may only be an intercurrent infection, or his immunity may be such that the malaria parasites are not actually giving rise to any symptoms at all. Again, the presence of one species of parasite, even if one is absolutely certain about its identity, does not preclude the presence of another. A worker who had the experience of only typical quartan malaria in the past, but who had not yet the recipient device for the detection of other species, might

Nevertheless, the presence of parasites cannot be ignored from the point of view of treatment, even if one is certain that they are not the cause of the whole symptom complex

Conversely there are many occasions on which one will fail to find parasites in a true case of untreated malaria, as any honest protozoologist will admit. The importance of making a definite protozoological diagnosis cannot be over-emphasized nor can one condemn too strongly the practitioner who assumes that all fever in a malarious country, or even in a malarial subject, is malaria. Nevertheless, after a very thorough though unsuccessful attempt to make a parasitological diagnosis, it is sheer folly to withhold treatment in a case in which other evidence points to malaria.

In the ordinary malarial attack parasites are usually present in the peripheral blood and are easy to find. They may however be scanty and it is easy to overlook the fine rings of the malignant tertian parasite in a thin film, a thick film will help in these circumstances. There are local variations to this rule, and in some localities the parasites in an ordinary case are very scanty in the peripheral blood. Other circumstances in which the parasites are often difficult to find are, (i) at the beginning of a primary attack, (ii) in residents in an endemic area who have acquired a degree of immunity to local strains, (iii) in chronic malaria with splenomegaly and (iv) after a few doses of an anti malarial drug.

Regarding the identification of the parasite, a worker often finds it difficult to distinguish between the different species, but after experience it is possible to find enough parasites to make a definite diagnosis. The parasites are however very common and may cause confusion

both directions, they may mistake true pigment as an artefact for it looks very like foreign matter superimposed on a cell, or they may mistake stain debris and dust for hemozoin pigment.



The increase in large mononuclears to 15 per cent will be a point of diagnostic value in some countries, but will not differentiate malaria from certain other protozoal diseases, e.g. kala-azar, and in any case may only indicate past malaria.

**Sternal puncture**—When the parasites cannot be found in the peripheral blood, it will often be worth using this method. In some observers' experience it has been proved a valuable supplementary diagnostic method.

the said disease in which As has been find parasites in a case of malaria, when therefore there is any suspicion in the mind of the physician that the fever from which the patient is suffering is malaria he should prescribe a course of the occasions on which this is possible alternative diagnosis a criminally in every case of fever occurring in a malarious country.

If the therapeutic test is decided upon, an adequate course must be prescribed and unless a definite diagnosis of some other disease is made

course

There are few cases of malaria in which the fever will not respond to

conditions. Therefore though the fever does not respond may very dangerous to make a positive diagnosis of malaria on the therapeutic test.

### DIFFERENTIAL DIAGNOSIS

The conditions which malaria may simulate are so numerous that a list cannot be written to deal adequately with the diseases from which malaria has to be differentiated. A justifiable amount of space, therefore, must be devoted to each, although the differential diagnosis of malaria has to be considered with the most important examples in each case, are given—

**Fever:** Short—Influenza, bronchitis, dengue, sandfly fever, relapsing fever.

psittacosis, malignant endocarditis, kala-azar, fevers, Hodgkin's disease, glandular fever, chronic inflammations.

**Splenic enlargements**—Leukæmia, splenic anæmia and syphilis, as well as the febrile diseases mentioned above, kala-azar, typhoid, etc.

**Anæmia**—Ancylostomiasis, hæmolytic and other anæmias.

**Cerebral**—Heat stroke, meningitis, apoplexy, epilepsy, diabetic coma, insulin shock, alcoholism, narcotic poisoning and trauma.

**Abdominal**—Dysentery, cholera, appendicitis, cholecystitis and liver abscess.

**Jaundice**—Weil's disease, yellow fever, infective hepatitis and catarrhal jaundice.

**Cardiac, pulmonary and nephritic conditions**

## TREATMENT

**Historical**—Cinchona bark which has been one of the indigenous medicines of South America probably for millennia, was first introduced into Europe as treatment for malaria according to tradition\* by the Countess of Chinchon the wife of the Spanish Viceroy of Peru, about the year 1638. The fame of this bark spread rapidly—for those days—through the world and it was apparently introduced into India about twenty years later.

The subsequent history of the drug in India is interesting for early in the nineteenth century it was almost entirely abandoned in the treatment of malaria. This surprising occurrence is easier to understand if one remembers that the diagnosis of malaria was clinical only and that there are many other fevers that simulate it. A long run of failures to get any response to cinchona therapy because the disease was not malaria might conceivably prejudice a physician against the drug. Also as powdered bark only was used and not the extracted bark, the treatment was not so effective as it is herefore in the use of the bark. A large number did not continue to use this invaluable drug surreptitiously. The treatment that was advocated in its place was heroic purging with calomel in particular and of course blood letting. Doses up to 60 grains of calomel were given and it was quite common for a patient to lose all his teeth from the mercurial gingivitis caused by this treatment.

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South America in 1860 and cinchona cultivation was started in India.

In 1866 the Madras Cinchona Commission was formed to investigate the relative value of the various alkaloids of cinchona bark. They came to the conclusion that quinine was the most useful alkaloid although the other crystalline alkaloids were also active in the treatment of malaria. This important and scientifically sound observation had very serious repercussions later.

The cultivation of cinchona flourished for some years in India and Ceylon until in the year 1887 Ceylon alone produced 16 million pounds of cinchona bark. This uncontrolled growth of the cinchona industry led inevitably to the disastrous slump which ended in the ruin of the cinchona plantations so that by the end of the century cinchona planting as a private enterprise had ceased in India. Java survived this slump and has enjoyed a virtual world monopoly in the cinchona industry ever since.

In 1931 a committee of the League of Nations Health Organization laid down a minimum standard for a cinchona-alkaloids mixture that was efficient and at the same time could be prepared from the hardier cinchona plants without the prior separation of the various alkaloids or the addition of quinine. This they called totaquina.

After the war of 1914-18 the German chemists stimulated by the fact that they had no colonies in which they could grow cinchona attempted to find a synthetic substitute for quinine and in 1926 Professor Schulemann produced the quinoline compound plasmochin which important though it is has only a limited application in malaria therapy. This was followed a few years later by an acridine compound which was given the name atabrin. The writer had the privilege of being the first physician to give a clinical trial to this drug. A Medical publication of the two first journal (Napier and Das Gupta).

\*The Countess of Chinchon tradition has now been exploded (Haggis 1941). The Countess about whom the picturesque story is told never went to Peru and her successor who did never had malaria never used the miraculous bark, and never returned to Europe. The true story appears to be that cinchona bark first reached Europe from Peru which was locally still retained.

**Cinchona requirements**—The world quinine requirements have been placed at 1,387,412 kilogrammes annually (League of Nations, 1932). In India, it has been conservatively estimated that to treat her one hundred million sufferers from malaria at least a million pounds of cinchona alkaloids are required. About 70,000 lbs of cinchona alkaloids, of which

Cultivation in the Philippines has been developing during the last few years. There is now little cultivation in South America, the natural home of cinchona. No other country produces cinchona in any significant amounts.

**The cinchona alkaloids**—Cinchona bark contains four crystalline and a number of amorphous alkaloids. The four former, quinine, cinchonine, quinidine and cinchonidine, all have anti-malarial properties. Of the individual alkaloids, quinine is undoubtedly the most valuable, as it is the most powerful and produces the least adverse by-effects. Of the other

the most useful is cinchonine if tract, and and is used crystalline samples of 50 per cent, as per cent of alkaloids

have a poor anti-malarial action and tend to make the tablets—a convenient form in which the mixed cinchona alkaloids are often given—hard and insoluble.

**Quinine salts**—Quinine base being very insoluble, the drug is usually given in the form of one of its salts. The most generally useful is the sulphate, though it is not very soluble in water and has to be prescribed with acid in the mixture. The bihydrochloride is the most soluble, but, making a very acid solution, it causes pain when given intramuscularly, and therefore the neutral hydrochloride salt is preferable for this purpose.

The dihydrobromide is conveniently soluble, but contains a smaller amount of the alkaloid and therefore 25 per cent should be added to the dose when this is prescribed in the place of the sulphate, and more when it replaces the bihydrochloride. It is reported to give rise to less cinchonism, but possibly this is accounted for by its lower alkaloidal content.

The ethyl carbonate is insoluble in saliva and therefore tasteless, but it dissolves in the normal gastric juice. It is not however fully absorbed and it is generally stated that 8 grams of the ethyl carbonate of quinine (euquinine) correspond to 5 grams of the sulphate.

The strength, solubility, and reaction of the commoner salts of quinine are as follows:—

Salt	Percentage of quinine base	Solubility in H <sub>2</sub> O at 25°C	Reaction
Sulphate	74	1 in 720	Neutral
Hydrochloride	82	1 in 18	"
Bisulphate	59	1 in 8	Strongly acid
Bihydrochloride	82	1 in 0.75	"
Dihydrobromide	60	1 in 6	Neutral
Ethyl carbonate	82	nil	Alkaline

There are many different species of cinchona, these vary in yield and in the amount of alkaloids. *C. ledgeriana* gives the highest

There are other plants e.g. the hybrids *C. officinalis* and *C. robusta*, that whilst they have a comparatively high alkaloid yield though short of that of *C. ledgeriana*, are very much harder than *C. ledgeriana*, and will grow over a much wider range of climatic conditions

**Totaquina standard**—The standard laid down for totaquina (introduced into the B.P. 1933) is that it shall contain at least 70 per cent of crystalline alkaloids, of which 15 per cent must be quinine, the amorphous alkaloids must be less than 20 per cent, mineral matter less than 5 per cent, and moisture less than 5 per cent. The cinchona febrifuge grown in the government plantations and prepared in the government factories in Bengal complies, for all practical purposes, with this standard. A recent analysis of a sample showed that it contained 32 per cent quinine, cinchonine 11 per cent, quinidine 1 per cent, cinchonidine 30 per cent, and amorphous alkaloids 15 per cent.

**Cinchona policy**—One of the main reasons that Java gained and has kept this world monopoly was that they have large areas of country that are particularly suited to the growth of the high-quinine yielding varieties of cinchona plant e.g. *Cinchona ledgeriana* and the world demand has during the last 80 years been almost entirely for quinine and not for the other alkaloids that might also be used in the treatment of malaria. It is natural that, if only one of the four available alkaloids is used and the others are more or less wasted the price of the one alkaloid will have to be greater than if all four were saleable for the planter must make his living. This has led to the price of quinine being comparatively high and the high price of quinine is an important adverse factor in malaria control in rural areas.

A committee of the League of Nations Health Organization studied this question of the high price of quinine. They decided that although no country could hope to produce quinine in competition with Java many could grow other cinchona plants that would produce a comparatively high yield of total alkaloids from which a preparation of mixed alkaloids of cinchona could be produced at a very much lower price than that of quinine. Another advantage would be that by growing these other cinchona plants on a large scale many poor countries could provide their own cinchona requirements and become independent of imported quinine. The committee realized that one of the reasons for the

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The unfortunate impression has arisen that cinchona febrifuge is a cheap and inferior substitute for quinine which is fostered on poor people who cannot afford quinine. This was of course true of some but not of all cinchona febrifuges and the international totaquina standard has given us a means of distinguishing between the good and the bad preparations. Only such preparations that are stated to be of 'totaquina standard' should be used.

The next step taken by this committee was the organization of experiments to show the relative efficacy of totaquina as compared with quinine. These experiments have shown that totaquina is very nearly if not quite as efficacious as quinine in the treatment of malaria. The writer's experience has been that it is perhaps even more efficacious in benign tertian infections.

India was only one of the countries which the committee of the League of Nations Health Organization had in mind but in no country could their work have more important repercussions if the government would take advantage of

the situation. Though India is not so fortunate as Java in her climate, *etc.* the cultivation of vast areas in which the government scale cinchona price of quinine is independent of imported quinine\* has nevertheless been found to grow, and to protect large tracts of the present become entirely

**The synthetic anti-malarials**—There is a very great future in this line of chemical research. The initial successes that have been achieved are very encouraging, and we believe that when chemists and pharmacologists can again turn their full attention to this subject more efficient and less toxic compounds will be found.

The first of the successful anti-malarial drugs to be synthesized was plasmochin (*BP* pamaquinum), this is *N*-diethyl-amino-isopentyl-8-amino-6-methoxy-quinoline. Originally introduced for the treatment of the malarial attack and the destruction of the asexual forms, plasmochin has now been found to be too toxic, in the doses in which it has to be given, for this purpose. It is however the only drug that has any appreciable direct action on the gametocytes, particularly those of malignant tertian. Also it enhances the action of quinine and mepacrine in completely eradicating a benign tertian infection and thereby preventing a relapse. In these two capacities, it acts in very small doses, far below the toxic level.

Cilonal, di-alkylamino-alkylamino-oxy-quinoline, a drug closely allied to plasmochin but much less toxic, has an action similar to that of plasmochin, it has however to be given in much larger doses to produce the same effect.

Another successful preparation is atebrian (*BP* mepacrine hydrochloridum), or dihydrochloride of 2-methoxy-6-chloro-9- $\alpha$ -diethylamino-8-alkylamino-acridine. This drug is less toxic, in normally non-toxic doses it destroys the asexual forms and controls the malarial attack, and has little and a... it is therefore similar in action to quinine.

There are now a number of preparations that are apparently identical with atebrian, *e.g.* crinodora, quinacrine, and recently British and American firms have also placed on the market preparations that are chemically identical with plasmochin, *e.g.* praquine.

**Mechanism of action**—The subject is not really ve... alkaloids act indirectly li...

reduce their numbers or schizonts, as these are

\* The writer as Editor of the *Indian Medical Gazette*, has for the last eleven years repeatedly urged the government to adopt a policy of extended cinchona growing and alkaloid distribution. Early in 1912 the Japanese invaded Java and India's external source of cinchona vanished. It has been possible to increase India's internal production to about 80,000 lbs a year which is about 8 per cent of the real requirements and 40 per cent of her average annual consumption for some years. Recriminations are useless but the writer feels that he may be allowed just this one 'I told you so'. The writer is informed that Mysore, Travancore and Ceylon are already starting cinchona plantations and cultivation in the Government of India plantations in Sikkim, Bengal and Madras is now being extended.

shortly after quinine administration. It is suggested that the action may be on the merozoites whilst they are free in the blood, either directly or by altering the charge on the red cells so that the merozoites are not attracted to, or are unable to enter, the red cells. The clinical evidence that the action of quinine is greater during the sporulating stage is inconclusive, the action on the sexual forms of *P. vivax* and *P. malariae* is poor and on those of *P. falciparum* is nil.

On the other hand the action of atabrin is a direct one: the molecule is attached firmly to the parasite which shows obvious signs of degeneration very shortly after the drug is given.

**Absorption and excretion.**—By whatever route quinine is given its eventual fate is much the same. Given by mouth to a normal individual it is absorbed very rapidly and appears in the blood within 15 minutes and in the urine within about half an hour; it reaches peak concentration in the urine in 5 to 9 hours and is practically all excreted within 24 hours.

Atabrin also is absorbed very rapidly, but most of it is fixed in the tissues; it is stored mainly in the liver, spleen and lungs. About one quarter of the total blood atabrin is in the plasma.

A plasma level of 50 to 80 microgrammes is considered desirable for effective treatment; this is usually reached within a few hours and is maintained if the newer intensive course of atabrin (see p. 105) is given, but plasma concentrations show wide individual variations.

By whichever route it is given atabrin appears in the urine very early, though not more than 3 to 4 per cent. of the dose taken is excreted by this route; excretion continues intermittently for many weeks after the patient has ceased to take atabrin. About twice this amount is excreted in the faeces.

## PRINCIPLES AND AIMS OF SPECIFIC TREATMENT

It will be advisable first to analyse our aims in the treatment of malaria, and we must consider treatment in the widest sense that is, treatment to prevent as well as cure the disease. The objects that we may hope to achieve by specific drug treatment can be placed under five headings:—

(1) *True causal prophylaxis*, the destruction of the sporozoites injected by the mosquito before they enter the red cell and commence their intra-corporeal cycle.

(2) *Clinical prophylaxis*, the administration of a drug that will prevent the infected person from suffering from an attack of clinical malaria, but without necessarily destroying all the parasites in that patient\*.

(3) *The treatment of the clinical attack.*

(4) *Treatment to prevent relapses.*

(5) *Gametocyte destruction in the cause of general prophylaxis.*

(1) *True causal prophylaxis* that is to say the destruction of the sporozoites injected by the mosquito before they enter the red cell and commence their intra-corporeal cycle.

There is at present no drug which will achieve this. Ten grains of quinine given daily for five days before and nine days after a person has been infected by a mosquito will not prevent the development of the parasite, nor will atabrin in full therapeutic doses followed by a daily dose of 0.1 gramme.

In an experiment carried out in London, in which some half-dozen well-known malaria workers took part, three daily doses of 0.02 gramme of

\*For this the army favours the expression 'suppressive treatment'. There are points in favour of this term provided that it is not used in a disparaging sense as it often is. The writer prefers the better established 'clinical prophylaxis'.

plasmodium (a dose which will sometimes produce toxic symptoms) were given for one day before and six days after the infective mosquito bite, and yet five out of six of these men became infected.

The discovery of a drug that will act on the sporozoites would mark a great advance in malaria therapy.

(2) Clinical prophylaxis, that is to say, the administration of a drug that will prevent the infected person from suffering from an attack of clinical malaria, but without necessarily destroying all parasites in that patient.

Now this can be done. A dose of 0.2 gramme (three grains of atabrin given twice a week, or a daily dose of six grains (five grains are sometimes insufficient) of quinine will usually keep a person free from clinical malaria, even in a very malarious place, for an almost indefinite period.

in the table below. In another group six grains of quinine were given daily to adults, and children were given smaller amounts, as shown in the table.

Ages, years	Atabrin grammes	Quinine
1 to 2	0.025	or 0.1 g. euquinine* (1½ grains)
3 to 4	0.05	or 0.2 g. euquinine (3 grains)
5 to 6	0.075	} or 0.3 g. quinine bihydrochloride
7 to 8	0.1	
9 to 10	0.125	
11 to 12	0.15	} or 0.4 g. quinine bihydrochloride
13 to 16	0.175	

A third control group received no specific treatment. The results of this prophylactic treatment are shown in figures 21a and 21b (Field, Niven and Hodgkin, 1937).

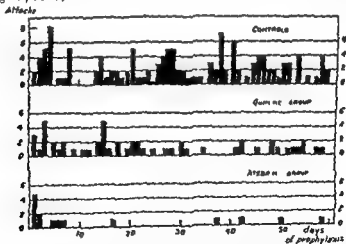


Figure 21a. Immediate effect of prophylactic measures.

It will be seen that in the atabrin series the malaria was controlled almost immediately and only an occasional case occurred. In the quinine

\*Euquinine or quinine ethyl carbonate is insoluble in the mouth and therefore tasteless, whilst it contains 82 per cent of the alkaloid actually more than quinine sulphate (74 per cent) its lower solubility in the gastro-intestinal tract makes it advisable to give it in the relatively larger doses indicated.

series the control of the malaria was slower but eventually it was largely effected

The important point however is that even in the atabrin group, they

suffered a similar attack of malaria almost immediately and nearly 50 per cent within two months

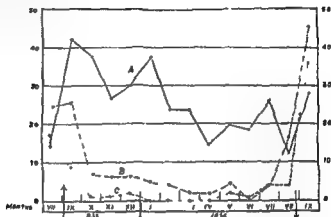


Figure 21b Monthly incidence of malarial attacks

	Number of subjects
A = Controls	91 $\pm$ 14
B = Quinine 0.4 gramme daily	91 $\pm$ 17
C = Atabrin 0.4 gramme weekly	103 $\pm$ 12

This is shown in figure 21 which gives the malaria incidence month by month for more than a year. It will be seen that when in the control group there were nearly forty cases monthly, in the atabrin group there were none or only one or two. However, directly the prophylactic treatment was withdrawn the incidence in the atabrin group rose to 37 and was actually higher than in the control group. Lamprell (1940) in a similar experiment in Assam obtained an exactly comparable result.

whom the infections were allowed to run their natural course and immunity was allowed to develop

It is thus apparent that drug prophylaxis in a labour force should only be carried out in special circumstances either as a stop gap whilst other anti-malarial methods are being organized or as a temporary measure to keep the largest possible number of workers in the field during a particularly busy time of year, this second reason will apply to armies operating in



malarious countries, and the adoption of this measure might well determine the success of a campaign

Ind. J. Med. Hyg. 1914, 1, 1. The action of the malarious mosquito is

other foreigner, is touring in a malarious tropical country, in such circumstances that he (or she) is likely to be bitten by a malaria-carrying mosquito, he should certainly take a prophylactic drug, and atabrin is in this case probably the drug of choice, it should be taken in prophylactic doses (p 98) during the whole stay in the malarious country and for a week after leaving it, after which a full therapeutic course should be taken (p 101)

(It should however be mentioned that though drug prophylaxis is most useful in the case of the casual visitor, it will actually be less effective in a non-immune individual than in one who has acquired some immunity through previous experience of malaria)

If this same person is residing for perhaps some years in a slightly malarious country he should not depend on drug prophylaxis, but take all other prophylactic measures (*vide infra*) to avoid infection, at the same time, if he is still running some risk of infection, drug prophylaxis should be used as an extra precaution, but in these circumstances, in view of our lack of knowledge of the effects of atabrin over a very long period, the writer would advocate quinine (six grains daily) again throughout the whole period of risk and for a short time afterwards

As the daily dose of quinine is not without its unpleasant and possibly mildly detrimental effects, it cannot be advocated lightly and in circum-

in tropical countries are liable to be unaccountably severe

There is no reason to suppose that prophylactic quinine is ever seriously detrimental, or that it increases the risk of blackwater fever occurring in a subject who takes it, as has been suggested, it is not the regular taking of quinine that is the predisposing factor in this serious sequel of malaria, but the frequent omissions to take it

... of the permanent settler in a malarious axis should ever be at-  
periodical attacks, which  
to allow them to work  
... liable to the general im-  
preventive measures

(3) *Treatment of the clinical attack*—In the very great majority of cases, the clinical attack can be terminated easily and rapidly by the administration of atabrin\*, quinine, or standardized cinchona febrifuge (B.P. tota-quina standard) given by mouth. Plasmochin\* has no place in treatment under this heading

\*The writer has used the words 'atabrin' and 'plasmochin' in preference to the official 'mepacrine' and 'pamaquine', as the former are at present more familiar but the references are not necessarily to the proprietary preparations with these names

Before discussing specific treatment, mention must be made of a recommendation of the Health Committee of the League of Nations, which has been severely criticized, but with which the writer is in part agreement. They recommend that in the initial attack of malaria the patient should be allowed to remain untreated for a few paroxysms in order that he may work up his natural immunity before he is given any anti malarial drug.

This suggestion is based on reliable experimental evidence and it is no doubt absolutely sound advice, in theory, but in practice it is seldom possible to do this, in most cases the patient's only desire is to be cured of the immediate attack, and if one insisted he would simply call in another doctor. It is, in any case, only advocated in benign tertian infection.

If cinchona or quinine are given the prescriptions should be —

R Totaqueum (or cinchona febrifuge)	g x	or R Quinine sulphatis	g x
Acidi sulphurici dil	miss xv	Acidi citratis	g xx
Magnesi sulphatis	g xxx	Aquam chloroformi ad	℥i
Aquam chloroformi ad	℥i		

One or other of these should be given twice daily in benign tertian infection and three times daily in malignant tertian infections and this dosage should be continued for seven days.

If atabrin is used 0.1 gramme (or  $1\frac{1}{2}$  grains) should be given three times a day for five days—or in severe malignant tertian infections this may be continued for seven days, but not longer.

For women and small or weak men, this dosage may be too high, and it may be advisable to reduce the 10 grains of quinine to  $7\frac{1}{2}$  grains, in each case the adult dose of atabrin is usually well tolerated.

Children both need and are able to take relatively larger doses of quinine than adults, the dose in grains is calculated as 1 to  $1\frac{1}{2}$  plus half the age of the child in years (e.g. give a well-nourished child of five years of age  $1\frac{1}{2} + \frac{1}{2} = 2$  grains). This is best given, twice or thrice daily according to the species of the infecting plasmodium, in treacle or honey, preferably in the form of the tasteless (euquinine), but if this salt is given the dosage must be increased by 50 per cent.

The total daily dosage of atabrin for children should be

1 to 2 years	0.05 gramme ( $\frac{1}{2}$ grain)	9 to 12 years	0.2 gramme (3 grains)
3 to 4 "	0.075 (1½ )	13 to 16 "	0.25 (4 )
5 to 8 "	0.1 (1½ " )	Over 16 "	0.30 (4½ )

The total dose is divided into two or three individual doses as is most convenient.

In the very great majority of instances oral administrations will be sufficient and effective. The reason for this is that when the drug is

is no response to oral administration and the various reasons for this are given below

(u) Faulty preparation of the tablets, that is, they may be insoluble through the presence of too much amorphous alkaloids, or because they are coated with some insoluble substance

(vi) Vomiting of the mixture or tablet

(vii) Failure of absorption by the gastric mucosa

(viii) Deception by the patient himself, or herself, on account of prejudice (pregnant woman) or malingering

The methods that can be recommended to circumvent some of these occurrences are to test the stock mixtures by means of the simple method originally suggested by Megaw, and to test the urine of the patient by the Tanret-Mayer test for the presence of quinine, or for atabrin by the method of Tropp and Weise (1933)

**Test for quinine in mixtures**—The reagent is made up as follows—Pure phosphotungstic acid—1 ounce dilute sulphuric acid—5 ounces and rectified spirit—12 ounces Place 2.5 ccm of the reagent into each of two narrow tubes add to one 0.25 ccm of the quinine solution to be tested and to the other 0.25 ccm of a control mixture containing the amount of quinine that the mixture was supposed to contain *eg* 10 grains to the ounce A precipitate forms which will settle and the two tubes can be compared in half an hour's time Any gross deficiency will be obvious

**Tanret Mayer test for quinine in urine**—The reagent is made as follows—Add a solution of 1.45 grammes of mercuric chloride in 80 ccm of undistilled water to a solution of 5 grammes of potassium iodide in 20 ccm of distilled water agitating the solution all the time To test the urine first boil and then filter it then add a few drops of reagent to 5 ccm of the urine an immediate precipitate forms if the alkaloid quinine is being excreted in the urine

**Test for atabrin in the urine**—Add 2.5 ccm of 80 per cent NaOH and 25 ccm of ether to 50 ccm of urine shake well allow the ether to separate pipette it off and to it add 5 ccm of N/10 hydrochloric acid The intensity of the yellow colour will be in proportion to the atabrin content of the urine

The question of administration of anti-malarial drugs by routes other than *via* the mouth can now be discussed

**Parenteral therapy**—There are two routes by which anti malarial drugs can be given parenterally (*para* = besides, *enteros* = intestine), namely the intramuscular and the intravenous, we will consider them together first

The points for and against these methods of administration may be considered under the following headings—

(i) **Necessity**—In certain circumstances parenteral therapy is essential as for example in unconscious patients and in cases where there is persistent vomiting

(ii) **Advantages**—The main advantages are that one gives the drug as soon as it has been taken, and further that it is not delayed by some workers,

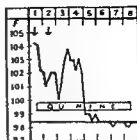
(iii) **Dangers**—These are not very great provided sufficient care is taken Intramuscular injections require scrupulous asepsis, and great care must be taken to avoid large nerves or neuritis or paralysis may be caused

In intravenous therapy, the injections must be given very slowly and the drug must be well diluted, or syncope and collapse may occur

(iv) **Abuses**—To give parenteral injections as a routine measure in the treatment of malaria is unnecessary and therefore a definite abuse

Even when parenteral therapy is indicated, it is seldom necessary to continue it beyond the first day, after this oral therapy can usually be instituted (see figure 22)

The intramuscular *versus* the intravenous route—On the subject of parenteral therapy, there are acute divergences of opinion in the ranks of the medical profession. Extreme views



and for a number of years there has been an 'official' ban on intramuscular injections. Textbooks, teachers, and even regulations have

Figure 22 Malignant tertian malaria heavy infection with vomiting two intravenous injections of quinine

dangers are all real though they may be very slight and the writer has seen both deaths and serious crippling result from intramuscular injections. Nevertheless there are in the tropics many observant and careful practitioners who do not hesitate to give intramuscular injections of quinine whenever they think that parenteral administration is indicated.

The writer's own point of view is that only in one in a hundred cases of malaria is the parenteral route indicated, and where it is indicated the intravenous route is preferable ninety-nine times out of a hundred. In the ten thousandth case he would not hesitate to give an intramuscular injection.

**Preparations and dosage—Intravenous—**Ten grains of quinine dihydrobromide in 20 c cm of normal saline or 5 per cent glucose repeated about six times a day. **Quinine** must be given by the intravenous route. **Quinine** must be given by the intravenous route.

This is given into the gluteus maximus, the vastus externus, the muscles at the angle of the scapula or the deltoid, or at the insertion of the muscle (0.3 of atabrin hydrochloride) in 9 c cm of distilled water, into one of these muscles.

\* Urethane acts as an analgesic and also increases the solubility of the salt.

(4) **Treatment to prevent relapses**—The big-stick methods which were losses of quinine over long periods, are no The average case of malignant tertian se after the ordinary curative dose of cinchona, quinine, or atebirin, but as relapse may be serious a second course after an interval of 7 to 10 days is usually advisable, the same remark applies to quartan infections. In benign tertian infections the relapse rate after quinine alone is usually high (70 per cent) and some special measures should certainly be adopted.

Following the line of thought started by Acton who showed that quinine acted best in an alkaline substratum, Sinton advocated the following routine procedure in the treatment of relapsing benign tertian malaria.

The two mixtures he used were —

Mixture A		Mixture B	
R Soda bicarbonatis	g lx	R Quininae sulphatis	g x
Soda citratis	g xl	Acidi citratis	g xx
Aquam ad	℥i	(or acidi sulph di)	xx)
		Aquam ad	℥i

**Course**—Give calomel in divided doses, i.e. 6 quarter-grain doses at half hour intervals at night, and magnesium sulphate at 6 o'clock in the morning, ℥ss to ℥i at 7-30, 9-30 and 11-30 a.m. give one dose of mixture A, followed by a dose of mixture B at 12 o'clock, at 3 o'clock give a dose of mixture A, followed half an hour later by a dose of mixture B.

From the 2nd to 5th days inclusive give three times during the day a dose of mixture A, followed half an hour later by a dose of mixture B.

On the 6th and 7th days give a dose of mixture A, followed half an hour later by one of mixture B, twice during the day.

This makes a total dose of 180 grains of quinine. Totaguina may be substituted for quinine without detriment to the treatment and where economy is to be considered this should always be done.

**Quinine plus plasmochin**—A very marked further reduction in the relapse rate in benign tertian malaria can be obtained by the addition of plasmochin to the quinine. The following dosages are recommended, the results obtained with each of these courses are about the same, but in either case the patients should be kept under observation for signs of intolerance to plasmochin.

Plasmochin 0.02 gramme plus quinine 10 grains twice a day

or plasmochin 0.01 gramme plus quinine 10 grains thrice a day, for seven days

**Atebrin and atebirin plus plasmochin**\*—Better results have been obtained with atebirin alone than with quinine alone, but, even with atebirin, plasmochin can be added with advantage in benign tertian infections.

Atebrin 0.1 g thrice daily, plasmochin 0.02 g once a day for five days—given together or separately.

There is considerable evidence to show that the combination of these two drugs enhances the toxic action of each, and patients should therefore

\*The writer has never seen any ill-effects from these combinations but recent experience of oth - than was previously suppo iter would therefore emphas he patient is under strict st ould only be used for the atment of relapsing benign quinine is not available

be kept under strict observation while these combinations are being administered. Many workers take it alone for five days and then to give twice daily for another five days. danger of toxic symptoms is undoubtedly prolonged.

Arsenic is a valuable adjuvant in the treatment. This can be given in the form of some arsphenamine preparation in three doses at 7 day intervals between two courses of cinchona febrifuge or quinine and alkalies, or as liquor arsenicalis added to a tonic mixture given after the specific anti-malarial course.

(5) **Gametocyte destruction in the cause of general prophylaxis**—This does not in any way help the patient for gametocytes can never again become asexual forms as long as they remain in the blood but if they are taken up by a mosquito they develop and the infection may be transmitted to others. It is therefore only in the interests of general prophylaxis that attempts should be made to destroy gametocytes.

It is in this capacity that plasmochin and the closely allied drug cational are unique. No other drug that we know will destroy the gametocytes of malignant tertian but this can be effected by a very small dose of plasmochin 0.01 gramme twice a day for three days. It may be given for the last three days of the quinine or atabrin treatment or after the course has been finished.

Mass treatment with plasmochin is a prophylactic measure suitable only in isolated communities but it is essential that every single member of the community particularly the infants should be treated and this is rarely possible (see p. 112).

**A comprehensive course**—We have considered treatment of malaria under the five headings separately, but in most circumstances one will

course should be given —

Quinine or totaquina gr x three times a day with plasmochin 0.02 gramme (or  $\frac{1}{2}$  grain) once a day for seven days followed by quinine or totaquina, gr x daily or 0.2 gramme atebria in a single dose on two consecutive days each week in either case the last mentioned dosages must be given as long as prophylaxis is to be maintained

**Recent experience**—This has abundantly confirmed the value of atabrin in all circumstances in which quinine was used hitherto. It has also tended to de-emphasize the toxicity of atabrin.

$$T_{\text{Th}} = \frac{\pi}{2} + \frac{\pi}{2} = \pi$$
[illegible]

for five days—a total of 15 grammes (240 grains) in a week

For causal prophylaxis (suppressive treatment), the daily administration of 0.1 gramme of atabrin for six days a week is now favoured. In order to reach the required blood level it must be given for two weeks before the subject enters the endemic area or alternatively an equivalent amount of atabrin must be given in a shorter period.

malaria to prevent relapses is being questioned nowadays. Although this subject must be considered *sub judice* the routine use of plasmoquin has been suspended in the American armed forces for the time being.

Much very important work on malaria has been carried out in Great Britain and America during the last few years but most of the results of this work are still considered of sufficient importance for the authorities in these two countries to prohibit their publication at present.

### Toxic Effects

The cinchona alkaloids—*Cinchonism* is the word used to indicate the mild toxic symptoms that follow the administration of these alkaloids namely headache and a 'fullness' of the head, buzzing in the ears, and deafness. Cinchonism is largely responsible for the unpopularity of the cinchona alkaloids amongst patients. The extent to which different individuals suffer from cinchonism varies very considerably, in this respect the personal factor is more important than the drug factor, though some alkaloids, *e.g.* cinchonidine, and some salts, *e.g.* quinine hydrobromide, are reputed to cause less cinchonism than others.

Taken in large doses all these alkaloids have toxic actions, and even in moderate doses these effects may be apparent in susceptible individuals. As we have noted above, quinidine is a heart depressant, and cinchonine is apt to irritate the gastric and intestinal mucosa and cause vomiting and diarrhoea. The other crystalline alkaloids may produce the same effects but are much less likely to do so. Quinine given in large doses produces

has also been reported in susceptible individuals.

Finally, some individuals have an idiosyncrasy towards quinine and even a very minute dose of quinine will precipitate toxic symptoms, these include anaphylactic-like symptoms, urticaria and other rashes, local swellings, and hæmorrhages, as well as those already mentioned. Such

case, this is another example of

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or five

the only drug of much  
caffeine citrate, gr 4  
ime is administered





(iii) *Symptoms following overdosage*, as noted below in (iv) and (v) in—(a) patients who have undertaken treatment themselves, (b) patients who have been first treated by a doctor and then continued treatment themselves, and (c) patients whose doctors have wrongly advised them through ignorance

(iv) *Mild by-effects which cannot harm the patient but about which the doctor should warn him*, e.g. (a) yellow discoloration, particularly of the skin, distinguished from jaundice by relative freedom of the sclerotics, and (b) a 'knocked-out' feeling (general lassitude) due to reduction in hæmoglobin which is dependent on destruction of parasitized red cells (it does not occur in the uninfected person receiving atabrin)

(v) *Personal idiosyncrasy following ordinary dosage*, e.g. gastric pains, headaches, giddiness, anorexia, hæmoglobinuria, epileptiform fits, and psychosis

Hæmoglobinuria is more usually associated with plasmochin administration

not serious  
 ' complete  
 a series of  
 ' where an  
 The author  
 has seen only two instances in his personal experience

(vi) It is known that plasmochin in large doses will give rise to symptoms (*vide supra*), it is suggested that the addition of plasmochin in even small doses, increases the toxicity of atabrin

**General management of a case**—Malaria not being a disease of the modern metropolis but of the tropical jungle, recommendations to treat it by putting the patient to bed in a high-ceilinged well-ventilated room with a night and a day nurse in attendance may not seem very reasonable to the practitioner who has to treat the vast majority of his patients where they lie, stand, or even march, and where the specific treatment will be the only thing that he can possibly afford to consider. Nevertheless, the message that such recommendations convey is the right one, namely, that the potentialities for serious development of the malarial attack should always be kept in mind, and that therefore the patient should, whenever possible, be put to bed and watched carefully for serious developments. The room should be darkened, and in the choice of clothing and bedding the drenching sweats that the patient may suffer should be remembered. If circumstances do not permit these to be changed frequently, then only flannel clothing and woollen blankets should be allowed, on the other hand, if proper nursing is available these are unnecessary and will not add to the patient's personal comfort

be g  
 kept  
 inte.  
 in the morning when necessary Aspirin and caennine can be given for head-  
 ache, or, if these fail to relieve it, phenobarbitone  
 only fluids should  
 bowels should be  
 omel at half-hour  
 subsequently salts

There is a popular theory that quinine should not be given at the height of the fever, there is no foundation for this, and specific treatment  
 decided upon Unless  
 the blood examina  
 al was made of the

ing a regular dosage

If the patient has become at all anæmic during the attack—this is by no means always the case—the appropriate treatment should be given for the anæmia. In the ordinary attack of malaria there has been no actual loss of iron from the body but nevertheless possibly because of previously existing iron deficiency so common in the tropics, iron given in large doses will usually improve the blood picture. The rational treatment is with liver extract, either by injection or by the mouth and autolyzed yeast products such as marmite. In the absence of facilities for accurate blood examination, treatment for both microcytic, i.e. iron, and macrocytic anæmia, i.e. liver extract and marmite, should be given. A useful prescription for the former is —

R Ferrous sulphate	grains 6	Liquor arsenicæ	minims 2
*Quinine sulphate	2	Dilute sulphuric acid	" 5
Magnesium sulphate	60	Peppermint water	to one ounce

To be taken three times a day

\* Omit at present in interests of economy

The treatment of the special case — It is scarcely possible to lay down hard and fast rules and to provide for all contingencies in the treatment of any disease, and this is particularly true of malaria with its great variety

*Atebrin*, in the form of the soluble atepirin musonate, is the drug of choice, this should be given intravenously in a dose of 0.125 gramme and repeated twice at one hour's intervals or intramuscularly as a single dose of 0.375 gramme. (The large dose is often given intravenously, but a few instances of ill effects have been reported)

If atepirin, or its equivalent, is not available, the next choice is quinine, 10 grains (0.6 gramme) of some soluble salt dissolved in 20 c cm. of saline and given intravenously. Finally if for any reason (e.g. the absence of a suitable syringe or of sufficient sterile solvent, or the difficulty of finding a suitable vein) the quinine cannot be given intravenously, it must be given intramuscularly, with the necessary precautions (*vide supra*). This dose should be repeated within a few hours if the acute symptoms do not subside.

It is possible that the circumstances may necessitate the parenteral route being used on the following day, for example, if vomiting occurs or persists, but by the third day it will, in almost every case, be possible to change to oral administration. This should be done at the earliest possible moment and the usual course completed.

Chronic malarial infections, the

results

Another method for reducing the size of the spleen is the intramuscular injection of sterile fat-free milk, at least 12 injections, from 2 c cm to 10 c cm, twice weekly.

The pregnant woman — The importance of giving the pregnant woman adequate treatment cannot be over-emphasized. Whenever possible it is

### PROGNOSIS

This must be considered from a number of different points of view, the immediate response to treatment, the chances of relapse, the immediate mortality, the indirect mortality, and the general effect on the health of the individual.

Prognosis will depend on the species and strain of parasite, the nutrition of the patient and his previous experience of malaria, the treatment given, and complications.

There are considerable differences in the virulence of the malarial strains in sular India. can be applied, but in peninsular virulence, whereas in the Himalayas are virulent. The first attack and the seriousness usually

When treatment is immediately available no one should die as the result of malaria alone but when a patient is first seen already unconscious his chances of recovery will be in the inverse ratio to the length of time that he has been unconscious and of the further delay in administering treatment.

In the partially immune adequate treatment will usually control the attack within 48 hours that is to say on an first day one paroxysm, on a single tertian

immune it is

paroxysms "

or five days (see figure 16) if the fever lasts longer than five days the efficacy of the treatment should be investigated (see p 101) and/or the diagnosis reviewed

The highest rate of immediate mortality is caused by *P. falciparum* (malignant tertian) infection it is particularly fatal in the infant and young child and in the pregnant woman *P. vivax* (benign tertian) and to a less extent *P. malariae* (quartan) infections will seldom prove immediately fatal even when no treatment is given

On the other hand relapses after adequate treatment are less common in malignant tertian malaria

Benign tertian malaria is probably little short of malignant tertian in the seriousness of its indirect effects especially on account of its marked tendency to relapse about 70 per cent of primary attacks relapse after an ordinary course of quinine

Quartan infections fall between malignant and benign tertian both in the severity of the attack and in the liability to relapse Kidney complications are said to be most common in quartan malaria but they also occur in malignant tertian

Anæmia is more likely to follow *P. falciparum* infections The failure of the blood picture to return to normal rapidly is usually an indication that expected However extract will often be though the infection

In a healthy well nourished person who receives adequate treatment convalescence is short and return to full activity may be expected within a week or ten days should frequent attacks or relapses occur at short intervals the period of convalescence will be considerably lengthened and still further so if the attacks are complicated by any bowel disease that interferes with nutrition

*P. ovale* infections are always mild and seldom relapse

#### PREVENTION

To appreciate the possibilities of malarial prophylaxis the reader must turn back to page 64 and consider the factors that determine malaria incidence If the cycle can be broken or even sufficiently weakened at any point malaria will be prevented

The methods by which the cycle may be broken can be discussed under the same four headings —

- A The malaria parasite
- B The mosquito vector
- C Man
- D The links between B and C

*A The malaria parasite*—In theory, the malaria parasite might be attacked (i) in the mosquito, or (ii) in man, we will consider how far it is possible to translate this into practice

(i) It is conceivable that, without destroying the mosquitoes, by the alteration of the local vegetation on which they feed, the mosquitoes' (non-blood) food might be made to affect adversely the malaria parasite in the insects' gut. Some work suggested that coumarin has been experimentally a suggestion has been in the development of the

This theoretical method of malaria control has a popular appeal which opportunist scientists readily take advantage of to intrigue non medical administrators, and much valuable time is wasted in refuting unscientifically based claims, so far all work on these lines has been entirely without result

(ii) In man the parasite can be destroyed by means of drugs at any but the sporozoite stage

Drug prophylaxis may be considered under two headings, *individual* and *community*

The question of *individual prophylaxis* has been discussed above (p 100) and it has been shown that clinical prophylaxis can be achieved but not true causal prophylaxis

and in time those in the community this treatment will lead much mischief will meanwhile of malaria control it is useless

On the other hand, the plasmochin group of drugs have a direct effect on the gametocytes and even a small dose of plasmochin, such as 0.01 g twice daily for three days, will destroy the gametocytes or at least make them non-viable. But if the patient still has an active infection, more gametocytes will be formed, so it is necessary first to destroy the parasites of the asexual cycle by treatment with cinchona or atabrin and then to destroy the gametocytes by means of plasmochin

The circumstances likely to be completely effective in a mixed community of gametocyte producers, and of any scheme of treatment. For a scheme to be a complete success, single individual must be treated. Again, the community should be an isolated one, and new arrivals should be subjected to treatment before they are allowed to reside with the established community

Drug prophylaxis is expensive, both in cost of the drug and in the labour involved. A 'blanket' treatment of the whole community will have

to be carried out, at first at frequent intervals. The results will not be immediately apparent for at the commencement of the scheme the mosquitoes that are going to produce the human infections or re infections during the next month or so are already infected. Later it will be possible to reduce the frequency of the blanket treatments, but the treatment of all those who suffer from an attack of malaria or who show gametocytes in their blood must be continued.

Therefore before a scheme of drug prophylaxis is undertaken one should be satisfied that (i) no other method of prophylaxis is practicable in the circumstances (ii) the community is sufficiently isolated (a) geographically to ensure that there will be no infiltration of infected mosquitoes from outside and (b) socially to make it possible to prevent casual night visitors and to control permanent immigrants (iii) it will be possible to bring every man woman and child living within the locality into the operation of the scheme (iv) the cost for the continuance of the measure can be met from the funds available and (v) if complete success is achieved the results will be worth this cost.

Whilst the occasions on which it will be worth carrying out a full

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attack of malaria amongst the inmates of servants the blood is cleared of gametocytes, and that new arrivals from malarious places are subjected to a routine course of treatment. The greatest danger is from servants and their children.

In conjunction with other anti malarial schemes it is always worth giving plasmochin and some workers have advocated a modified form of 'blanket' treatment in conjunction with anti mosquito measures but it is very doubtful if in most circumstances the results are worth the additional cost of such a measure.

On the other hand

it is not

the

Anti larval measures — The methods adopted can be discussed under the following headings —

(i) *Elimination of unnecessary collections of water*, these will mostly

tanks wells, and ditches and around fountains and water taps

creation of man made breeding places, railways are the classical example which engineers make unnecessary

(iii) *The control of treatment of necessary local water collections*, of these common examples are cisterns wells fire buckets and fountains and ornamental water

(iv) *The elimination or treatment of large scale but avoidable collections of water* these may be due to water logging natural or brought

about by interference with natural drainage by the building of railways roads, etc., or may consist of irregular collections of water in dead rivers or in river beds during the drier seasons of the year

(v) *The control of larval breeding in large essential collections of water, lakes, reservoirs and tanks, rivers, irrigation channels and streams drainage channels, and rice fields*

In the case of water collections of the first three groups it is not of mosquito reasons, but carry other diseases and are at the least a cause of annoyance to man. The methods of dealing with these will usually be obvious. Where they cannot be eliminated, they should be dealt with in other ways, wells and cisterns must, for example, be kept covered, or the water emptied periodically, in many cantonments in India, a 'dry day' is instituted once a week, on this day all uncovered collections of water must be emptied.

Water collections of the last two groups present the real problems of malaria control by anti-larval measures about which so much has been written, it will only be possible here to enumerate some of the methods that have been adopted, and readers must refer to the many useful books on this subject for details (e.g. Covell, 1941)

The methods of eliminating the large collections of water or controlling breeding in them are almost without exception expensive, and it is therefore first essential to make sure that these potential breeding places

dissecting a large number of mosquitoes at the right time of year. This common sense procedure of utilizing accumulated knowledge, to which has been added the results of local investigation, regarding which mosquito

malaria, on the tenth occasion it may have common sense and another vector and thereby defeat one's object. This is where the expert's superior knowledge will come in, but where nature is concerned no one is omniscient.

For some of the very worst set-backs in anti-malaria campaigns, the have come to a new or listening to the to apply methods that they had previously employed with success in other countries. It is therefore essential to make a very careful study of local conditions before giving any advice on larval control methods. Each country in the world presents its own particular problems, and if one cannot learn from some of the books or papers useful books in which

There are numerous methods of draining unnecessary collections of water, and circumstances will dictate which of these is likely to be the most fruitful. Or it may be cheaper to treat the breeding places with larvicides.

the rate of flow, intermittent irrigation, flooding, periodic sluicing or varying the water level, shading or letting in the light by biological means, e.g. changing the flora and fauna, introducing larvivorous fish or deterrent aquatic vegetation (largely theoretical) or by poisoning the larvae or their food supply, with oil, chemical poisons, e.g. DDT, Paris green or copper sulphate or vegetable larvicides, e.g. pyrethrum or derris.

**Anti imago measures**—The principle of this method of control is not simply to reduce the number of mosquitoes, nor even to kill the infective mosquitoes, but to *prevent the local malaria vector from becoming infective by shortening its average duration of life*. The most striking demonstration of its effectiveness is that in all cases when spraying is carried out properly the infectivity rate among mosquitoes immediately drops to nil.

Recently much more attention has been paid to this method particularly in Europe and cooler countries where the mosquito enters a house and tends to remain there for long periods if left undisturbed and where it is much easier in closed rooms to destroy them. However this method has been used extensively in hotter climates even under conditions where it is more difficult to close the rooms on account of the much more open nature of the habitations and considerable success has been claimed. It is particularly applicable to private houses, barracks and offices but can be applied to the huts of the poorer inhabitants. It is also employed usefully in public conveyances, railway carriages, omnibuses and aeroplanes.

The methods of destruction employed are swatting, trapping, fumigating and spraying, the last named usually being the method of choice.

Spray killing of adult mosquitoes is now recognized to be one of the major methods of control in anti malaria campaigns. It is the only one of the anti imago measures of real practical importance. It is the only measure which can have an *immediate* effect on the course of a malaria epidemic which has already started. It is the only anti malaria

troops operating under modern war conditions.

Covell considers that the Punjab epidemics provide an excellent

sprayers to meet an emergency.

The most effective sprays have a basis of kerosene and the majority contain pyrethrum, there are many proprietary brands but a useful and not expensive spray may be made from 19 parts of kerosene and one part of concentrated (2 per cent) extract of pyrethrum.



There are certain advantages in a spray with a watery base; the

also (1912) have recommended the following spray:—

Twenty pounds of pyrethrum flowers are extracted with 12 gallons of white kerosene. This will make 10 to 11 gallons of concentrated extract, the extract is mixed with water in the proportions of 1 to 7, and 20 grammes of sodium lauryl sulphate (or 'Gardinol') are added for each gallon of emulsion.

### Technique of Spraying

All apertures should be closed as far as possible before spraying, and should remain closed for 20 minutes thereafter. It is, however, usually impossible to do this completely, in which case it is necessary to use rather more of the spraying solution. It is more economical in the end to use a greater quantity of spray, rather than to waste time in stopping up apertures with sacking, etc. Even when the structure sprayed consists of a thatched roof without sides, numbers of mosquitoes can be killed by directing the spray upwards into the thatch. Before spraying the inside of a hut, the outside should be systematically sprayed under the eaves. The sprayer should in all cases be directed upwards.

**Period of spraying**—Systematic spraying should commence a fortnight before the malaria season is expected to start and should be continued throughout the transmission period.

**Time of spraying**—Mosquitoes almost invariably feed during the night. *A. minimus*, for instance, usually feeds between midnight and daybreak. After feeding, the mosquito remains in a sluggish condition during the early stage of digestion of its blood meal. It is therefore advisable to commence spraying in the early morning as soon as after daybreak as possible.

**Frequency of spraying**—The efficacy of the method is in direct proportion to the frequency with which spraying is done. It is better to spray once a week than to spray once a month. The rate among the local population is preferably thrice, a week. It is better to spray as often as possible.

**Amount of spray required**—This is about half an ounce per 1,000 cubic feet, which is about the size of the average one-roomed coolie hut. Allowance must also be made for spraying other suitable anopheline shelters, such as cattle-sheds and store-rooms.

**Sprayers**—Power-driven sprayers are the most effective, and are also the most economical in consumption of spray, in labour and in time of spraying. The apparatus used is identical with that employed for the spray painting of motor cars, etc. The following models have been found suitable:—

1 De Vilbiss portable petrol-driven power sprayer, type NH-616, 1/2 H.P., mounted on trolley, cost about Rs 605/-

2 De Vilbiss portable electric (universal) sprayer, type NC-615, 1/4 H.P., mounted on trolley, cost about Rs 330/-

Excellent results can also be obtained by the use of hand sprayers although there is no type at present available which is at the same time effective in operation, durable, easy to operate, and economical in consumption of spray.

### Freon aerosol "bombs"

These are small hand-grenade-like metal containers in which there is a mixture of pyrethrins—1 per cent sesame oil—2 per cent, freon (dichloro-difluoro-methane)—97 per cent. Since the vapour pressure of the freon provides the necessary spraying power it is only necessary to remove the cap to operate the spray. Freon is itself

It seems possible that DDT  
Pyrethrum will grow in mos-  
flowers have been found to go  
flowers, though not as high as

There are probably unexplored biological methods of destroying adult

was found, did not feed on mosquitoes

**C Man**—The elimination of man would break the malaria cycle. Short of this drastic procedure, it is however possible to take some action under this heading

**Increasing immunity**—Immunity is seldom complete, but if a community is by previous experience of malaria well immunized against a particular strain—the term *salted* is used in this connection—it will mean that the adult in the community seldom suffers from an infection heavy enough to cause a febrile reaction or to lead to the formation of any considerable number of gametocytes, he will thus not himself become a casualty nor will he be a prolific source of infection to the mosquitoes in the locality. In this way, immunity acts as a brake on the intensity of the malaria incidence in any community and any measure that raises this immunity is an anti-malarial measure, just as, conversely, anything that lowers it is a malarigenic factor

A method of malaria control

(see figure 23)

Other measures of control under this heading will include the careful selection of labour forces so that immune populations are not mixed with non immune, and children are excluded as far as possible

The question of employment of *salted* labour is a very complicated one. Some employers of labour advocate it strongly and others criticize it. The ideal labour force in a



Figure 23 Decrease in mortality from malaria in Italy over a forty year period (Illustrate 1969)

**D The links between the mosquito (B) and man (C)** D- 2-2  
that the mosquito ve  
occur The methods  
may be considered as

**General**—In the choice of sites of towns, villages, settlements, coolie lines, camps or even houses, the question of the proximity to uncontrollable mosquito-breeding grounds, as well as to uncontrollable human reservoirs of infection, should always be considered. Whenever possible the opinion of an expert malariologist should be obtained. In the past, millions of pounds could have been saved by this simple precaution, and mistakes are still being made. Unless he has made a special study of malariology and had some personal experience, a medical officer should refuse to express an opinion on a matter of this kind, and, whenever any considerable amount of money is involved, he will be well advised in any case to insist on the opinion of an expert malariologist being obtained.

Small bodies of men, hunting parties, prospectors and engineers, 'commando' troops, going into malaria infected country should be warned to avoid native villages for their temporary night halts as they would a plague-stricken village, they should also view with equal suspicion any clearing in bush or jungle which has obviously recently been the site of an encampment.

Where the village or residence is already established there are some biological methods of interception that have been advocated, these include the planting of alleged deterrent vegetation, *eg* neem and eucalyptus trees, castor-oil plants, lavender and clover, and the use of cattle to deviate the attentions of the mosquitoes from their human sources of blood supply *ie* zooprophylaxis (*see* p 70 Zoophilism). In practice, all these biological methods have proved disappointing.

Another measure is the screening of barracks, hospitals, and houses. In some countries this is practised extensively and its popularity is increasing, it must always be considered, whenever it is practicable, as an additional measure. Dr D P Curry, who has directed the mosquito control work for many years in the Panama Canal Zone, recently wrote, 'in spite of all our sanitation, we still must insist on screened living quarters, and screened offices for those persons who must work at night'. It does not add much to the cost of a building to include screening in its construction. Combined with systematic spray-killing, screening may be considered a major method, in places where more comprehensive methods of malaria prevention are impracticable. It is however necessary that in ordinary circumstances and does not interfere too much with the entrance of fresh air

this reason the method most generally useful, 3 gauge (SWG), this keeps out all mosquitoes

\* buildings are the avoidance of dark during the day and the provision of screening on the personal methods of

prevention

The personal methods of protection include the use of repellents for smearing over the uncovered parts of the body, the use of mosquito killing sprays (vaporisers), the use of means of protecting the legs *eg* gaiters, and mosquito nets whilst sitting at table, veils and gloves, and mosquito nets

Innumerable repellents have been suggested from time to time but in India pyrethrum was preferred before the introduction of the new insecticide, DDT which will probably prove cheaper

Covell recommends the following formula — Extract of pyrethrum (2 per cent) 20 c cm Oil of citronella 5 c cm Gum tragacanth powder 4 grammes Water 80 c cm

*Note*—If a stronger extract of pyrethrum can be obtained it should be used. If the European tragacanth is available the quantity should be 5 to 6 grammes

A great improvement has recently been made in repellents and some of the best in use today are effective for 24 hours with one application

Mosquito nets should be 25/26 mesh of 30/s cotton. These trade terms will mean little to the ordinary man they are arrived at by fantastic methods of calculation with which the reader need not burden his memory. They do not mean that there are 25 holes to the inch linear or square actually a net of this specification has about 12 holes to the linear inch and 150 to the square inch

Similarly the mosquitoes must be prevented from feeding on an infected person and in a hospital or other institution the patient suffering from malaria should always be made to use a mosquito net as a measure of protection for the community

*Amelioration of the effects of malaria*—In certain circumstances it has been found that the practical difficulties of preventing malaria are so great that preventive measures are scarcely worth attempting. In these circumstances the question of organized treatment to ameliorate the effects of malaria should be considered. Bonification referred to above is really a measure of this nature though it may achieve mosquito control as a side line

In many places in India there is little hope of eradicating malaria and the next best measure is to provide cheap or free treatment for the individual sufferer not with any hope of actually eradicating the disease but in order to mitigate the damage that the infection does. This is especially true in the epidemic areas in the Punjab where for a short time during the year conditions may be extremely favourable for transmission and where anti-larval measures would be impossible or prohibitively costly. By studying climatic conditions that precede these epidemics sanitarians have learnt to foretell epidemics and with the help of special epidemic units, now arrange for the mass treatment of the population by free distribution of cinchona alkaloids and by other means. The possibilities of combining this treatment campaign with spray killing of mosquitoes is discussed above

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ascertains the extent to which malaria is present in the locality or if a large area is involved in different parts of that area how it affects different sections of the population the time of year when it is most prevalent what are the vectors what are their sporozoite rates and where they breed and in fact all that can be ascertained about the epidemiology of malaria under the various headings under which it has been discussed above

*recommending any procedure*  
that one should have all the  
early every case some form of  
1. By a malaria survey one

The extent of malarial endemicity can be judged from the 'parasite rate' or the 'spleen rate', or preferably both. To find out the parasite rate, thick and thin films will have to be taken of a representative group of the population, and examined by the methods described above, from this examination the infestation rate and the average parasite count can be calculated, of the whole and of different groups of the population, but there are many refinements in this type of work and the reader is referred to one of the books devoted to this subject (e.g. Covell, 1939).

The calculation of the spleen rate has similarly been reduced to a fine art (Covell\*, information that give invaluable children between the ages of two = between these years the spleen's reaction to malarial infection is more constant than at other ages. The children should be lined up against a wall and the sizes of their spleens ascertained by palpation. The children are placed in five classes according to the sizes of their spleens, class I, not palpable—0, class II palpable but not beyond the costal margin—p, class III, up to three—this but —+++ enlarge concerned, rate, as

follows —

- Healthy areas—below 10 per cent
- Areas of moderate endemicity—from 10 to 25 per cent
- Areas of high endemicity—between 25 and 50 per cent
- Areas of hyperendemicity—constantly 50 per cent or over

In conclusion the successful control of malaria requires a very wide

is decided upon. The ex should never be ignored, that the methods have =

The economic aspect will always be paramount in this imperfect world. One's first thoughts must be, how much will it cost and will it pay? An accurate answer to the first half of the question should be given, but for the second a long view must be satisfied with a promising 4 years before the good effects appear. A quicker return though they may be content to wait a year or two, but on the other hand, a commander of an army, or an engineer in charge of the construction of a railway, road or bridge, may have little interest in what happens next year and only be concerned with next week or next month.

\* Christopher's method has many advantages, including the important one of allowing for differences in the size of the children and is very easy in practice though from the description it appears complicated. It consists in marking the 'apex' of the umbilicus—on a table  
1th Bulletin

## MALARIA THERAPY

The origin of this form of treatment was the observation that though syphilis is as common in most malarious countries as it is in the temperate zones neuro-

This form of treatment attracted a very great deal of attention in Europe and in England a mosquito farm was organized under the auspices of the Ministry of Health for the purpose of conveying malaria infection easily and safely to those who were to be treated by this measure

Besides being a very successful form of treatment—about half the patients suffering from general paralysis thus treated were considerably improved by the treatment—it provided us with a very valuable opportunity for studying experimentally certain aspects of malaria transmission and treatment. The most important workers in this field have been James and later Sinton in England Cuca in Roumania and Boyd and later Shannon in the United States

The infection may be transmitted by the agency of laboratory bred mosquitoes directly by their bite or by dissecting out the salivary glands and inoculating the sporozoites or by the injection of infected blood (see p 71). In the latter case 2 to 5 c.c.m. of defibrinated blood from a patient with malaria is inoculated intra

produced the incubation period of inoculation malaria is shorter the course tends to be milder there are fewer early and no late relapses and it is much more easily controlled by treatment

In malaria the incubation period is shorter the course tends to be milder there are fewer early and no late relapses and it is much more easily controlled by treatment

An example of this difficulty occurred recently in the author's experience. A patient with an antecedent malarial infection was given a course of treatment with the species

carried out a few more quartan parasites were found but the infection was still mainly benign tertian. As the infection was showing signs of dying out inoculation was not delayed further. Twelve days after the inoculation the tabetic patient developed fever which was found to be due to a heavy *malignant tertian* infection and within a day or two very energetic anti-malarial treatment had to be given to save his life.

The patient should be allowed to have 8 to 12 paroxysms before the infection is terminated by anti-malarial treatment. If the rigors are too severe and occur

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## BLACKWATER FEVER

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**Definition**—Blackwater fever is a special manifestation of malaria, characterized by hæmoglobinuria

The pathology and the clinical picture in this condition are so characteristic and so different from those of the ordinary malarial attack that it is justifiable to consider it as a separate disease entity, though it is now generally accepted that plasmodia are the sole causal organisms

**Historical**—The main historical interest is that although malaria has been known for twenty-five centuries, with the exception of some doubtful references in Hippocratic medical writings there is no reference to the blackwater syndrome in medical literature until a little over a century ago, when Boyle (1831) referred to it in his *Fevers of West Africa*. Scott (1939) draws attention to the fact that the literature of blackwater fever has shown a marked national grouping, about the middle of the century, writers reported the disease in Madagascar and in other French possessions in Africa, after another decade the Greeks took up the subject, and these are followed in turn by Italian, American, Dutch (Java), German (1890) and eventually British medical writers

This late historical appearance of the disease has been used to support various claims regarding its aetiology, for example that it must be a disease *sui generis* or at least caused by a special plasmodial strain and alternately that it must be due to the use of quinine. In view of our knowledge of the present writer that the increase of the disease in the last century was associated with the widespread foreign invasion of tropical territory that occurred at this time and that beyond this the observation does not point to any special aetiological factor

### EPIDEMIOLOGY

Blackwater fever occurs only in highly endemic malarious countries (or amongst persons who have lived in such countries) and its seasonal incidence is always correlated with the season of highest malaria incidence, so that its epidemiology is the epidemiology of malaria, with some special features

**Geographical distribution**—As it occurs in nearly all the intensely malarious countries in the world, no separate map is necessary, it does not however, occur further north than 40°N or further south than 20°S. In Europe it is most prevalent in Greece and Macedonia and a few others.

In India, the worst blackwater fever areas are in the Doonars and Terai (at the foot of the Himalayas), Assam, the Chittagong hill tracts, Santal Parganas, Chota Nagpur, and the Madras Presidency, and in Burma in the North and South Shan States

Whilst these are the localities where the patient acquires his predisposing tendency to blackwater fever, the attack may develop in some non-malarious country, it is quite common, for example for those returning from the East to be attacked in London

**Local distribution**—It occurs mainly in areas where malignant tertian malaria is endemic throughout the year. In India, and in many other countries, it is prevalent where more civilized races come into close contact with primitive peoples, that is to say, on the borders of jungle tracts. In places it also has a local distribution that does not seem to be solely explained by high malaria endemicity, for in other equally malarious districts it does not occur, this local carrier species of mosquito which endows it with special

**Individual incidence**—In blackwater fever areas, the disease is very rare amongst the local natives, but occurs amongst foreigners, in India, it seldom occurs in any one area, and amongst those who have

had a previous attack

People of all ages and both sexes may be attacked

### ÆTIOLOGY

The ætiological factors must be considered under two headings, (A) *predisposing*, and (B) *precipitating*

Of the predisposing factors, (i), (ii) and (iii) are essential, and (iv) and (v) important additional factors. The incidents that may precipitate an attack can be placed in three groups, one alone is sufficient but there may be a combination of precipitating factors

(A) *Predisposing factors* — (i) A plasmodial infection is the first essential. The disease is nearly always associated with malignant tertian infections, but instances have been reported where apparently pure benign tertian or pure quartan infections have given rise to blackwater fever

(ii) Absence of established immunity to all local malaria strains, such as is acquired by indigenous inhabitants of a locality

(iii) Previous subjection to intense malarial infection over a period of at least a year

(iv) Irregular and inadequate treatment of these attacks

(v) A previous attack of blackwater fever, this is evidence of individual susceptibility for about 10 per cent of blackwater fever subjects suffer a second attack

(B) *Precipitating factors* — (i) Quinine administration this has a double action as it stimulates the action of the reticulo-endothelial cells to destroy parasites and incidentally red cells, and quinine itself, especially as an acid salt also has a slight hæmolytic action. The other anti malarial drugs may act in the same way, but are not so frequently reported as the precipitating factor, possibly because, in the case of atabrin the main action of the drug is a direct one on the malaria parasite itself

(ii) Cold (*cf* paroxysmal hæmoglobinuria), fatigue (increase of sarcolactic acid), alcohol, arsphenamine and certain other toxic drugs, and trauma

(iii) X-ray applications to the spleen, which stimulate the hæmolytic cells of the reticulo endothelial system

The mechanism of hæmolysis — The exact physiological process by which old and worn out red cells are removed from the circulation is a question not yet finally settled, but it is probably an intracellular, rather

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cold which assists the action of the hæmolysin already formed (cf paroxysmal hæmoglobinuria)

(bilirubinuria)

Theories regarding the cause of blackwater fever—Even if we accept the description given above as the mechanism of the attack it does not really explain why it occurs in some people and not in others. One sugges-

but against it is the occurrence of blackwater fever in therapeutic malaria—a few instances of which have been reported—where the virulence of the strain used is known. The alternative suggestion, that a benign strain

Some years ago the writer tentatively put forward two suggestions these were based on both epidemiological and experimental evidence (Napier and Campbell 1932). The first was that rapid passage through a series of susceptible hosts raised the virulence of a previously normal strain of malaria parasite and the second somewhat contradictory to the first that the virulent strains of plasmodium which are harboured by the immunized people of jungle tracts when transmitted to non-immunes (non immune to that particular strain) caused a virulent infection. In the experiments on which these theories were based by passage of the Simian plasmodium *Plasmodium knowlesi* (later named as such) from a monkey of the *Silenus* *rus* species in which it was dormant and over shadowed by a *P. m.* infection through a series of *Silenus rhesus* monkeys we produced a virulent infection associated with hæmoglobinuria\* in the latter species (and incidentally drew the first attention to this plasmodium species which has played such an important role in experimental malaria ever since).

There is little support for the former theory but the latter dovetails in with the general theory enunciated above.

Other theories that have been put forward have either been disproved or died through lack of support. These include the theory that it is the result of acidosis enhanced by giving acid salts of quinine, or the excessive formation of sarco lactic acid by muscular exertion, this theory is weakened by the observation that acidosis is not constantly present in blackwater fever. That it is a pure quinine intoxication has now been disproved by the occurrence of blackwater fever in people who have not taken quinine so frequently that this theory can have few supporters. The finding of

\* This hæmoglobinuria is not strictly comparable to blackwater fever as it is not associated with any hæmoclastic crisis but is simply the result of excessive destruction of red cells by the plasmodium infection possibly combined with a low kidney threshold for hæmoglobin in the host.

a spirochætal infection in blackwater by one or two observers has not been confirmed, nor has any other specific organism been found, though there are some who still consider that it is a disease *sui generis*

In the writer's opinion the 'phenomenon' of blackwater fever requires no explanation beyond that already outlined in the previous paragraphs, if allowance is made for varying individual susceptibility

### PATHOLOGY

This is basically the same as that of malaria, but the pathology is different from the malarial one, and is based on the fact that the parasites which they

In blackwater fever, the most characteristic and extensive changes are in the kidneys. The free hæmoglobin in the blood passes through the glomeruli and reaches the tubules where, the environment being more on the acid side, acid hæmatin is precipitated, and the tubules become blocked

The kidneys are large and dark, the tubules are blocked with brown debris and hæmoglobin casts, and there is cloudy swelling and degeneration of the tubular endothelium. The liver is stained an intense yellow (hæmosiderin), and there is central necrosis of the parenchyma cells. The gall-bladder is filled with thick viscid bile. The spleen is enlarged and almost black (hæmoglobin pigment) on section, there is general endothelial proliferation and there are areas of focal necrosis in the malpighian corpuscles

**Blood**—The blood of the disease shows a marked anaemia. The hæmoglobin count drops to about 10, and of a single attack there are signs of anaemia is usual.

Parasites are by no means always found in the peripheral blood at the time the patient comes under observation, but an investigation in the blood in 73 per cent of the cases on the day of the

In a series of 20 cases in northern Bengal, Bhattacharya (1941) reported finding parasites in the blood in six out of ten cases in which there had been no previous quinine treatment

**Biochemistry**—The proportion of hæmoglobin in the blood is about 10, and a marked hyperbilirubinaemia is produced by the blood (Fairley, 1941)

There is marked hyperbilirubinaemia in severe cases, the indirect van den Bergh test indicating an amount as high as 40 mg per 100 c cm of blood

The blood urea rises as high as 450 mg even in non-fatal cases and in cases of renal failure this may be higher. The cholesterol content of the blood is considerably reduced. The alkali reserve may be as low as 30 c cm  $\text{CO}_2$ .

level of the col and ever the colour of the urine lightens to a light brown and finally a yellow, which may persist in the urine for many days. The urine is markedly acid. If it is shaken, the presence of hæmoglobin is shown by a pink foam.

The test for albumin shows a heavy cloud.

In severe cases bile is present but this is usually masked by the hæmoglobin. Methæmalbumin is not excreted by the kidneys and does not therefore appear in the urine.

Microscopically, there is much brown debris and hæmoglobin casts, but there are few red cells.

The fæces may show pleocholia for a few days.

### SYMPTOMATOLOGY

**Prodroma**—Mild febrile attacks associated with a yellow discoloration of the sclerotics or frank jaundice are sometimes noticed for a day or so before the real attack, but as a rule the onset occurs with dramatic suddenness.

**Onset**—Sometimes the first sign of the disease is that the patient finds his urine bright red, usually, however, the syndrome supervenes during an apparently ordinary attack of malignant tertian malaria, there is headache, very severe prostration with pain in the kidney region, nausea, and vomiting, and then the patient notices that his urine is coloured red.

Bhattacharya (*loc cit*) reported the first appearance of hæmoglobin in his 20 cases as follows—

Day of fever	No. of cases	Day of fever	No. of cases
1st day	3	4th day	5
2nd day	3	5th day	2
3rd day .. ..	7	Total	20

**The course of the disease**—There is usually a single severe hæmolytic explosion, all the damage being done in a matter of a few hours, but there may be a series of hæmolytic crises, in which case the prognosis is poor. The temperature is high at first but tends to be very irregular later, the pulse is very rapid, and the blood pressure is low, later, the blood pressure may rise with the onset of renal failure. The headache, nausea, vomiting, and prostration may be marked and may continue for some days. There may be marked weakness and a thready pulse.

Meanwhile the urine will have passed through the stages of port-wine colour and be almost black but in severe cases anuria will set in, and,

though it is not uncommon for urinary secretion to commence again, even after 48 hours, azotæmia ('uræmia') as the result of continued anuria is a common cause of death. Even polyuric cases may prove fatal.

The spleen is usually markedly enlarged and tender (but may be temporarily reduced during an attack as a result of the expulsion of reserve blood), the liver is tender and the gall-bladder may be felt, jaundice appears early, on the second day, and is usually unaccompanied by itching.

Recovery may be rapid, or on the other hand the symptoms may increase and the patient die of heart failure, or cerebral symptoms—irritability, delirium and coma—may appear, in such a case he usually shows early signs of collapse, the breathing becomes Cheyne-Stokes in character and death soon follows.

A marked degree of anæmia, which is usually macrocytic, and general debility place very definitely *infra*)

Relapses are common

the mild (more or-  
(c) the continuous  
inuric, and (e) the  
hæmorrhagic

#### DIFFERENTIAL DIAGNOSIS

The conditions from which blackwater fever has to be distinguished can be grouped under the following headings —

(a) Hæmoglobinuria caused solely by the taking of quinine or plasmochin (the existence of this condition is now questioned), 'march' hæmoglobinuria, paroxysmal hæmoglobinuria (an interesting condition dependent on the incompatibility of an individual's plasma and red cells imitated by  
" chiasfava-  
caused by  
and as a  
etary substances, an example of  
blackwater in other symptoms  
(*Vicia faba*) in excess (Luisada,  
1941)

Certain drugs and other substances may produce a red coloration in the urine, which could be mistaken for hæmoglobin, for example, beetroot, cochineal and, amongst the drugs, amidopyrin, phenolphthalein, and prontosil-rubrum.

Hæmoglobinuria is also imitated as a means of malingering (in India, pan, commonly chewed by Indians, particularly women, added to the urine makes a fair semblance of hæmoglobinuria). The final test for hæmoglobin is by means of a spectroscope, the hæmoglobin bands are easily recognized. This can be done with a pocket spectroscope.

(b) Hæmaturia, due to various local causes, oxaluria, new growth, stone, etc., yellow fever, hæmorrhagic diathesis and other conditions where hæmorrhages occur from mucous membranes.

(c) Jaundice, due to any cause but especially yellow fever, or Weil's disease, in both these conditions it develops later and tends to progress

## TREATMENT

General principles — The patient should be treated and nursed on the warm and moist should

bicarbonate as they report that it also helps to reduce hæmolysis

Anti-malarial drugs — In the majority of cases there are no parasites in the peripheral blood at the time the patient is seen after the attack, and in these circumstances no anti-malarial drug is necessary. If parasites are still present atabrin in the usual doses (see p 101) should be given

Symptomatic — For anuria if intravenous therapy fails hot fomentations of the loins and frictions with mentholated citrate of lime a few

Sodium sulphate, 180 per cent of the anhydrous salt in distilled water, given intravenously by the drip-feed method, up to a litre, should be tried, if the above methods fail

The diuretics that are most likely to be of value are caffeine and sodium benzoate given by intramuscular injection in doses of 4 grains or caffeine citrate gr iii or diuretin gr x three times daily given by the mouth

Vomiting can sometimes be stopped by giving the patient ice to suck, if not, 1 ccm of adrenaline diluted with an ounce of water should be given by mouth but if this and other simpler means of controlling vomiting fail, an injection of morphia (1/10 grain) and hyoscine (1/200 grain) may be given

For cardiac stimulation, camphor in oil cardiazol and coramine are the drugs of choice

As a purgative, calomel should be given in divided doses ( $\frac{1}{4}$  grain half-hourly up to  $1\frac{1}{2}$  grains)

'Specifics' — A large number of specifics for the treatment of black-water fever have been advocated. Many of these have acquired a considerable local reputation but none has been shown to possess definite anti-hæmolytic properties *in vitro* (Gupta *et al*, 1942)

plant has been prepared which has been shown to possess definite anti-hæmolytic properties *in vitro* (Gupta *et al*, 1942)

Also  
in India  
tried in



A line of treatment more recently introduced is with cortin, or its synthetic equivalent, desoxycorticosterone acetate, 25 mg immediately and 5 mg 4 hourly, combined with vitamin C in maximal doses intravenously or intramuscularly, and cholesterol 15 grams 4 hourly by the mouth. Even in this case, the exact rationale is not clear and it is doubtful if cholesterol taken by mouth increases the blood cholesterol appreciably, but the writer has seen uniformly satisfactory results with this routine during the last few years. Again, however, no scientifically controlled series of experiments of sufficient number to carry any weight have been reported upon.

**Blood transfusion and other hæmâtinic treatment**—Transfusion has

suffering from anoxæmia after a crisis, transfusions of cross matched whole blood up to 400 c cm in the first instance are certainly worth considering. They must always be given slowly. Oxygen will always be helpful at this juncture.

if possible

**Diet**—Diet should be fluid and of low nitrogen content during the acute

that have accompanied the attack.

**Convalescence**—A special word of warning is necessary in convalescence, as sudden heart failure is common, some physicians insist on all patients remaining strictly in bed for at least 10 days after the hæmoglobinuria has completely stopped.

## PREVENTION

The prevention of blackwater fever is the prevention of malaria and the subject does not require separate discussion here (see pp 111-119).

The drug prophylaxis is also the same as for malaria but, in view of the undoubted action of quinine in precipitating an attack of blackwater fever, the question whether it is advisable to take prophylactic quinine in a blackwater fever area will naturally arise. Whenever this point has been investigated it has been found that the disease is far less common amongst those who take prophylactic quinine regularly than amongst those who take it just when they happen to remember it or not at all. Thorough treatment of the mal

group of drugs

If the old remedy *Vitex peduncularis* lives up to its new promise it might provide a drug that could usefully be employed prophylactically in a blackwater fever country, especially by blackwater fever subjects, whenever they feel a malarial attack coming on.

## PROGNOSIS

One of the principal characteristics of blackwater fever is the great variability of the severity of the disease from place to place and from time to time in any one place this is why the results of any particular form of treatment are so likely to be misleading. When large series are reported the death rate usually varies between 10 to 20 per cent but in a smaller series a death rate of 40 per cent is not at all uncommon and conversely death rates as low as 5 per cent are reported.

The prognosis deteriorates with each successive attack. There is a popular saying in blackwater fever districts that 'one often recovers from the first attack seldom from a second and never from a third'. This is of course not true but it conveys the right message and as there is some evidence of individual susceptibility which is possibly enhanced by an attack it is advisable for a blackwater fever subject to seek employment in some other locality.

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**Addendum**—Recent examination of the current explanation for the anuria namely damage to the kidney as a result of excreting the large molecule (68 000) haemoglobin and precipitation of acid haematin in the

epithelium is far more sensitive than the glomeruli. It is believed that acidosis which is not constant cannot alone explain the changes and that acid base electrolyte water balance must be considered as a whole. Dehydration on extrinsic and intrinsic is an important factor.

The practical point here is that treatment by excessive alkalization may do more harm than good. Whole blood transfusion has for many years been used successfully in treatment even when the degree of anaemia did not seem to demand it and though it is known that the haemoglobin thus given is often haemolyzed. It seems possible that better results might be obtained with plasma transfusions combined with oxygen inhalation.

# LEISHMANIASIS

## CLASSIFICATION OF LEISHMANIA INFECTIONS

The diseases in man caused by protozoa of the genus *Leishmania* Ross, 1903, can be considered under the following three headings:—

(i) Visceral leishmaniasis, or kala-azar, in which the causal organism, *Leishmania donovani*, is spread by the blood and invades practically all the tissues in the body except those of the nervous system

There is an infant leishmaniasis of kala-azar and in the next the equal organism generally . . . . . Similarly . . . . . variety of . . . . . from *L*

Post-kala-azar dermal leishmaniasis, in its numerous forms, is a late sequel to the generalized infection, in this condition the parasites (*L donovani*), having disappeared from the viscera, are confined to the skin and cause non-ulcerative skin lesions unaccompanied by any general symptoms

(ii) Cutaneous leishmaniasis or oriental sore, in which the infection is localized in the skin and causes ulcerative lesions, in this condition the infection is apparently not spread by the blood-stream, but, rarely, extension has occurred along lymphatic channels, *Leishmania tropica* is the causal organism

(iii) Mucocutaneous or South American leishmaniasis, or espundia in which there is a primary invasion of the skin, as in oriental sore, followed, sometimes after the original sore has healed, by a specific ulceration of the nasal, buccal, and pharyngeal mucous membranes, the spread of infection is presumably by the blood-stream, although the blood infection has not been demonstrated in this disease, *Leishmania brasiliensis* is the causal organism

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The position was clarified when in 1903 the causal organism, now classified as *Leishmania donovani*, was found in the spleen of a soldier at Dum Dum, a place where the disease had contracted by Donovan in the smears made

A disease known as 'ponos', which had been recognised in Greece and other Mediterranean countries for many years, was shown to be caused by the same organism

Kala-azar was first diagnosed in China by Aspland in 1910 and in the Sudan by Boufield Thomson, and Marshall (1911)

#### EPIDEMIOLOGY

**Geographical distribution**—The disease has a widespread distribution in the Old World, and has been reported from South America, but up to now not from Oceania

In Europe the most heavily affected areas are in the south of Italy, and certain Mediterranean case has been reported in V. It is comparatively common in the provinces of Catalonia and other Greek islands, isolated cases have been reported from many other Mediterranean ports. At Catania 1,424 cases were diagnosed in a period of ten years, and in Hydra 39 per cent of the deaths among infants during one year were said to be due to this disease, but in most of the other places it is only sporadic in occurrence (see figure 24)



Figure 24 Map showing Kala-azar distribution (shaded) in the Mediterranean area

In the Mediterranean area the disease is confined almost entirely to infants and young children

In North Africa the same infantile form of the disease occurs along the Mediterranean littoral, in Morocco, Algeria, and Tunis, the incidence being highest in the last-named

There is another endemic area in the Sudan, in Kassala and the Blue Nile district, and cases have been reported from Abyssinia, northern Kenya, and a few other places in tropical

Africa, but only in the Sudan endemic focus has there been any serious incidence of the disease, here kala azar, which is not of the infantile type but has an age distribution comparable to the Asiatic form of the disease came into prominence during the fighting in 1940-41 in Abyssinia and on the borders of the Sudan, and a number of Indian troops were infected.

In India the distribution is extensive, but the limits of the endemic areas are well defined, the disease being confined to the eastern side of the peninsula. Intensely infected isolated villages have been found in the extreme south near Cape Comorin. There is a steady incidence of a few

hundred cases each year in Madras city. The coastal areas are then free up as far as the Ganges delta. The whole of the plains of Bengal are heavily infected. The endemic area spreads along the Ganges plain into Bihar where the incidence is still high, and to the eastern side of the United Provinces as far as Lucknow, where the incidence gradually tails off, its westerly extension being checked by the dry areas. In Bihar it is confined to the Ganges valley, being limited on the north by the Himalayas and on the south by the low laterite hills of the Bihar plateau. In a north easterly direction the endemic area extends along the Brahma putra valley into Assam, which province is heavily infected as far as Sibsagar, at present sporadic cases only occur further east. From the main Bengal focus the endemic areas extend into eastern Bengal and Sylhet but further extension is prevented by the high mountain ranges which divide India from Burma. It will be interesting to see whether the opening up of direct communications between India and Burma across these mountains will lead to an extension of the disease into Burma on analogy the writer believes that it will not (see figure 25).

In China the endemic areas are nearly all north of the Yangtse river and are mainly along the line of the grand canal in the provinces of Kiangsu, Shantung and Chih-li up to Peiping and further north into Jehol and Fengtien in Manchuria. Cases have also been

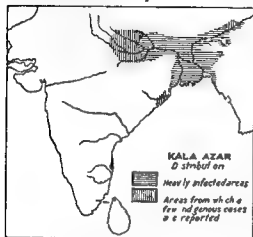


Figure 25 Map showing kala azar distribution in India

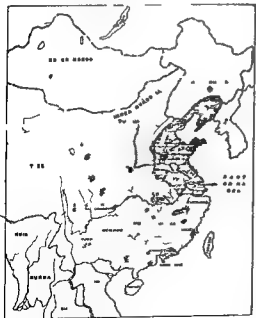


Figure 26 Map showing kala azar distribution in China shaded areas

canal in the provinces of Kiangsu, Shantung and Chih-li up to Peiping and further north into Jehol and Fengtien in Manchuria. Cases have also been

There are endemic foci in Transcaucasia and Russian Turkestan. It has recently been shown that kala-azar is widespread in the tropical zone in South America and a few cases have been reported from Argentina. Isolated cases have been reported from here during the last twenty years, but on the whole the reports were received with scepticism, until light was thrown on the subject by the yellow-fever viscerotomy service in Brazil and Argentina, out of 47,000 viscerotomies, leishmanias were found in 41 specimens. Subsequent clinical investigations in some of the infected areas brought to light a few cases of kala-azar. Nearly all the leishmania-infected viscerotomy specimens and most of the clinical cases came from the north east corner of Brazil between Para and Bahia, but a few kala azar patients were also found in the Chaco district of Argentina. The cases were sporadic, and entirely unconnected with one another (*see figure 27*)

**Epidemic features**—In most countries in which it exists, kala-azar is sporadic in its occurrence,



Figure 27 Map showing kala-azar distribution in South America

subject to exacerbations of an re effective treatment was given, where rises and falls in incidence appear to have had a definite periodicity of about fifteen to twenty years. In an endemic area, there was usually a widespread increase in incidence over the whole area, which lasted for three or four years, then there would be a gradual fall, but the disease did not disappear, and even in the trough of the wave the incidence did not drop to less than one-third or a quarter of the incidence at the top of the wave.

The character and periodicity of these epidemic waves are probably being disturbed by the extensive treatment campaigns that have been instituted in the most heavily infected provinces, Assam and Bengal, since the beginning of the last epidemic. The last epidemic wave started in 1917 and reached its peak about 1923. On previous experience another wave is overdue by at least five years, but provincial health returns give little indication of it, except in the province of Bihar, at the periphery of the endemic area, where no treatment campaign was instituted, and here the increase in the incidence of the disease has recently alarmed the health authorities.





**Age and sex incidence**—In so far as the age incidence of the disease is concerned the endemic areas are sharply divided into two groups. In the Mediterranean areas the disease occurs among infants and very young children 93 per cent under the age of five years and is rare among adults. On

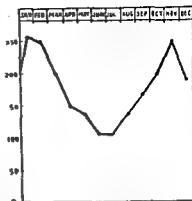


Figure 23. Month of onset of kala azar based on over 2000 cases seen in Calcutta

years this difference in the age incidence has led some workers to regard kala azar in the two regions as being distinct and to use the term 'infantile kala azar' for the disease as it occurs on the Mediterranean littoral. The age distribution, however, is the only notable point of distinction. Even in India kala azar occurs among infants, we reported a case of an infant of less than eight months with well developed kala azar of about four months duration.

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### Age and sex incidence of kala azar

Age group	Males	Females	Total	Per cent per quinquennial age period
Under 5 years	27	26	43	12.40
5 years but under 10 years	48	57	105	27.13
10 " 15	60	29	89	23.00
15 " 20	26	20	46	11.88
20 " 30	30	37	67	8.65 × 2
30 " 40	16	11	24	3.10 × 2
40 " 50	2	11	8	1.03 × 2
TOTAL	204	183	387	

There is no evidence that either sex is the more susceptible most of the collected figures show a preponderance among males but when the errors of selection are eliminated the difference practically disappears.

**Race, caste and class**—There is also no evidence of racial or class immunity. In India Europeans and Asiatics are equally liable to infection.

when living under comparable conditions. The disease is rare among better-class Europeans and Indians living in well-built and well-ventilated houses, but it is very common among poorer-class Europeans and Anglo-Indians. In some mixed villages the disease seems to predominate among those living in the Mohammedan and Indian Christian quarters, the Hindus being comparatively free.

### ÆTIOLOGY

**Causal organism** — *Leishmania donovani* is a protozoon of the family Trypanosomidae, other members of the genus are *L. tropica*, the causal organism of cutaneous leishmaniasis or oriental sore, and *L. brasiliensis*, the causal organism of South American leishmaniasis, or espundia. The parasite of the infantile type of kala-azar has been named *L. infantum*, but there is little evidence that this organism differs in any way from *L. donovani*. The parasite that causes leishmania infection in dogs has been called *L. canis*, but there is evidence that, in some instances, at least, this also is identical with *L. donovani*.

### Morphology and Life-cycle of *Leishmania donovani*

Two forms of the parasite are known: the non-flagellate or 'round' form, the Leishman-Donovan body, in which form it occurs in the body of its mammalian host, and the flagellate form, in which it occurs in its arthropod host (*vide infra*). The development from the round form to the flagellate form will also take place in culture medium.

**Non-flagellate form** — The non-flagellate form is an oval or round body with an average diameter of about  $2\mu$ , the breadth in the oval form being about three-quarters of the length. It consists of cytoplasm containing a nucleus which is more or less round and a little less than  $1\mu$  in diameter, a parabasal body from which springs a rhizoplast, and a vacuole.

The Leishman-Donovan body

is found in the blood

In the blood  
which they are

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parasites are  
China and in  
the lymphatic

glands, but in India it has been difficult to demonstrate them in this site.

Viable parasites in this form have been demonstrated in the faeces (Mackie, 1914), in the urine (Shortt, 1923), and in nasal secretion (Forkner and Zia, 1934), their presence in these excreta and secretions must be looked upon as accidental, depending as it does on the separation of small pieces of mucous membrane with its submucosa, which is not the usual result of leishmania infection but is due to some coincident secondary infection.

Whilst the immediate viability of these parasites in the stools and nasal secretions has been demonstrated by animal experiment, there is no reason to believe that, outside the body, they remain viable for more than a matter of hours. A pure growth of leishmania has been obtained from

sterile urine, but in the presence of other organisms the leishmaniae are rapidly killed

**Flagellate stage**—The flagellate form shows several morphological features. It is a fusiform organism with a flagellum  $15\mu$ , the breadth  $0.5\mu$  to  $2.0\mu$ , and the body of the flagellate consists of leish, a parabasal body situated about midway between the nucleus and the anterior end of the body of the parasite a rhizoplast and flagellum springing from the parabasal body and a vacuole lying between the parabasal body and the anterior end of the body of the parasite (see figure 29 and plate B)



Figure 29 Structure of Leishmania in the round and the flagellate or leptomonad stages

N = nucleus  
P = parabasal  
R = rhizoplast  
V = vacuole  
F = flagellum

**Culture**—A number of different media have been used for the cultivation of leishmania but by far the most satisfactory is NNN or Senekjia's

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its flagellum

It has been shown that in susceptible animals Chinese and Syrian hamsters, *Cricetulus griseus* and *Cricetus auratus*, infection can be caused by the introduction of either the round or the flagellate forms by the

pi  
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infra)

### Transmission

**Historical**—Since the discovery of the parasite forty years ago many investigations have been undertaken to discover how kala-azar is transmitted from one person to another. Innumerable hypotheses have been propounded and

when living under comparable conditions. The disease is rare among better-class Europeans and Indians living in well-built and well-ventilated houses, but it is very common among poorer-class Europeans and Anglo Indians. In some mixed villages the disease seems to predominate among those living in the Mohammedan and Indian Christian quarters, the Hindus being comparatively free.

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The Leishman-Donovan body is found in the endothelial cells and large wandering macrophages in all parts of the host's body. The parasites are therefore found in the tissues and organs richest in reticulo-endothelial cells, i.e. in the spleen, liver, bone marrow, lymphatic glands and in the submucosa in all parts of the respiratory and intestinal tracts. In the blood they are also seen in the polymorphonuclear leucocytes, in which they are

seldom found in the parenchymatous cells of the organs. In China and in the Sudan they are said to be found in large numbers in the lymphatic glands, but in India it has been difficult to demonstrate them in this site.

Viable parasites in this form have been demonstrated in the faeces (Forkner, 1906). The faeces, when looked at in small pieces, usually result in leishmania infection but is due to some coincident secondary infection.

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N = nucleus  
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**Culture**—A number of different media have been used for the cultivation of leishmania but by far the most satisfactory is NNN or Senekjies (see p 164) medium. The former is a simple saline agar preparation to which about one third fresh rabbit's blood is added while the agar is cooling but is still in the fluid state. The blood and agar are then mixed by rotating the tube between the palms and sloped. The hydrogen ion concentration need not be adjusted as the blood is an efficient buffer the pH is usually about 7.0 but good growth will take place between pH 4.7 and 8.0.

**Survival and pathogenicity**—The flagellate form is a very delicate form and contamination with bacteria will rapidly kill a culture. The flagellate will not survive in water or soil but survives in sterile milk for a few days. When injected subcutaneously it rapidly rounds up and loses its flagellum.

It has been shown that in susceptible animals Chinese and Syrian hamsters are highly susceptible to the parasite.

infra)

### Transmission

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The finding of parasites in various excreta and secreta has naturally led to the suggestion that direct transmission from man to man might occur in nature, but the epidemiology of the disease negates these suggestions. To take one point only, the strict geographical limitations of the disease seem to indicate some more complicated biological process which demands special meteorological and physiographical conditions. This led to the suggestion that leishmaniasis were the natural parasite of some insect and that man was an intermediate host, the bed-bug, the flea, and several flying blood-sucking insects were considered and in turn discarded after experimental work had yielded negative results.

The workers at the Calcutta School of Tropical Medicine were impressed by the fact that of the various blood sucking insects under suspicion, the local distribution in Calcutta of the sand fly, *Phlebotomus argentipes* corresponded most closely with the distribution of kala-azar and that the geographical distribution of this particular species of sand-fly in India as far as it was known again appeared to correspond with that of kala-azar. They showed that under the conditions in which kala-azar was most prevalent, this sand fly was a persistent human-blood feeder and in a series of experiments with laboratory bred *P. argentipes* they showed that when these flies were fed on a kala-azar patient, a heavy flagellate infection developed in about 25 per cent of the flies so fed (Knowles Napier, and Smith, 1924), they also found that this same degree of development did not occur in other species. Other workers confirmed this observation, and Shortt Barraud, and Craighead (1926) showed that the infection passed forwards in the sand fly, eventually infecting the buccal cavity.

Later experiments have shown that these sand flies become infected after feeding on persons who have had kala-azar and have recovered from the visceral infection but are suffering from that interesting sequel of the infection, post-kala-azar dermal leishmaniasis (see p 149), even in cases in which the skin lesions are so ill developed as to be scarcely perceptible (Napier et al., 1933).

Isolated transmissions of the infection to Chinese hamsters *Cricetus griseus*, by means of the bite of the sand fly were effected (Shortt et al., 1931 and Napier et al., 1933), and the matter was left at this stage for some years. More recently, Smith et al. (1941) have demonstrated that the survival and progress of the infection in the sand fly depend largely on whether it takes a second blood meal or subsists on fruit or plant juices. In the latter case, a large percentage of the infected flies develop a massive infection of leishmania which blocks the pharynx and buccal cavity (*vide infra*), when these 'blocked' flies are fed on a susceptible animal, infection almost invariably takes place.

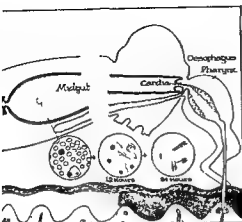
Finally, Swaminath, Shortt and Anderson (1942), by feeding flies according to the technique devised by Smith have transmitted the disease to five out of six human volunteers who were natives of, and lived throughout the period of the experiment in, a non-endemic area.

In China the sand-flies associated with kala-azar transmission are *P. major* and *P. major* var *chinensis*, one or other is prevalent in all the endemic areas of the disease in that country and they have been shown to be efficient carriers (Young and Hertig 1926). In Italy and the Mediterranean area generally both *P. major* and *P. perniciosus*, especially the latter, are thought to be transmitters, one or other is prevalent in all the endemic areas and Adler and Theodor (1931) have thirteen species of sand fly of the Sudan there are believed to be the transmitter.

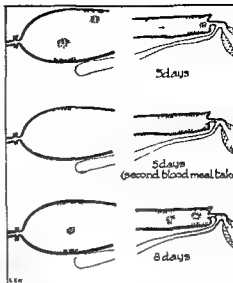
The future which the sand flies may follow along these lines regarding the distribution and incidence of kala-azar.

or fruit juices on the parasite in the future investigation remaining anomalies

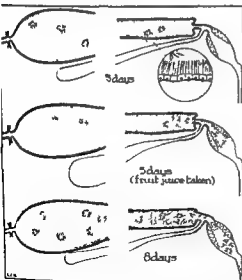
The development of the parasite in the sand fly and the mechanism of transmission—The parasite is taken into the mid gut of the sand-fly with its blood meal, the round form becomes a flagellate form, and active



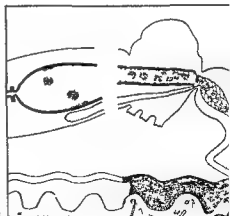
When the sandfly takes infected blood into its midgut, the blood is digested and leishmaniasis forms are freed. These develop into leptomonad forms, multiply by binary fission, and move forward in the fly's intestinal tract.



If the fly takes a second blood meal too early, leptomonad growth is interrupted and a relatively light infection results.



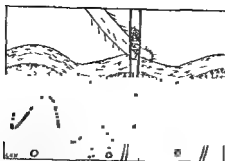
If, however, it takes fruit or plant juice, the leptomonad growth flourishes and the cardia, oesophagus, and pharynx of the fly become blocked with leptomonad forms.



When this blocked fly attempts to feed, it is unable to draw blood past the solid plug of leishmaniasis forms. During its struggle to obtain some of these are detached and are injected into the skin.



# PLATE II (Pathogenesis of Kala-azar)



Leptomonad forms are injected by a 'blocked' sandfly into the skin



In the skin they immediately lose their flagella and round up. Some are taken up by macrophages others by polymorphonuclears



The former multiply, but the latter are digested and disappear



There is a local reaction to the presence of leishmania in the form of an aggregation and proliferation of tissue and blood

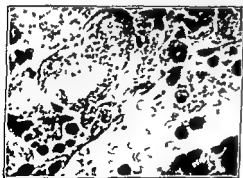


The parasites continue to multiply slowly until the parasitized cell bursts

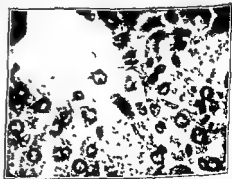


Parasites are then taken up by other macrophages

Eventually some of the parasitized cells reach the circulating blood and are carried to the viscera.



In the spleen rapid multiplication occurs and the reticulo-endothelial cells become heavily parasitized. In the figure a parasitized cell is seen escaping into the spleen sinus, this will circulate for a time, but will eventually come to rest in some other organ or tissue where if this is rich in reticulo-endothelial cells further parasitization and proliferation will take place



In the liver Kupfer's cells are seen heavily parasitized, the parenchyma cells escape infection, but appear to be compressed by the hypertrophied Kupfer's cells

division occurs by the third day the infection has reached the cardia by the fifth day the parasites have passed through the œsophageal opening into the pharynx, and by the seventh day the parasites may be found in the buccal cavity. If about the fifth day the fly takes another blood meal the flagellate infection is retarded and remains comparatively light. If on the other hand it takes fruit or plant juice the infection is not retarded but progresses rapidly to the stage where the œsophagus and pharynx are blocked with a massive flagellate infection.

When a blocked fly feeds on man before it can take any blood this solid block of flagellates has to be ejected and it will naturally be injected into the wound made by the sandfly's proboscis. There is a little local reaction to this inoculum of flagellates; some flagellates will enter the blood stream where they will probably be destroyed but others will be taken up

**The sand fly vectors**—The three most important species are *Phlebotomus argentipes* Ann & Brun in India, *P. major* var *chinensis* Newst in China and *P. perniciosus* Newst in the Mediterranean area. They are all very similar in their habits.

*Phlebotomus argentipes*—This is a dark brown medium-sized sand fly 2 mm to 3 mm long. On the thorax the dorsum is black and the sides light yellow; the wings are rather broader than those of most species and the tarsi are white. According to Sinton this species is not found outside India. It has a widespread distribution in India but is most prevalent in Bengal and Assam where it can be found at any time of the year but is most prevalent during and immediately after the monsoon (see figure 25 plate A).

*Phlebotomus major* var *chinensis*—The colour is variable, dull greyish to bright golden yellow. The abdominal hairs are more or less erect dorsally and are a uniform golden grey with very strong silvery light. The disc of the wings has a bluish iridescence; the eyes are black and the legs are sometimes darker than the abdomen which is clothed with long recumbent hairs and has tufts of longer upright ones on the dorsal surface. This species is closely allied to *P. argentipes* from which it is however easily distinguished.

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*P. papatasi*

**Sand fly prevalence**—In Bengal there is a small rise in the sand fly incidence between the cool months and the hot months. The sand flies are found in the largest numbers in the houses from wind currents. They are also found in the houses when these are damp and ill ventilated and have a broken or unpaved floor and especially in rooms with a window opening on to a courtyard where ducks, chickens or goats are kept. In the houses with mud walls and thatched roofs, sand flies are not any but but they are found in these walls which are not so easily found comparatively

These sand-flies breed in any earth that contains an admixture of nitrogenous matter, the larvæ are found in the corners of broken floors

Bengal obtain their water-supply)

**Relation to live stock**—They seldom breed far from their food-supply and when the choice is between bovine and human blood they choose the former, on the other hand, they seldom feed on other domestic animals or birds. This observation is based on the examination and identification of the blood meals of many sand-flies of this species by the precipitin method (Lloyd and Napier, 1930). The deduction is therefore that cows attract sand-flies to the vicinity but at the same time withdraw the flies' attention from human hosts and are therefore a mixed blessing, on the other hand other animals attract sand-flies by providing a suitable environment for their breeding but do not withdraw their attention and are therefore wholly noxious. This fits in with our observations on the distribution of kala azar in towns and mixed villages, the inevitable cow in the Hindu homestead seems to provide some degree of protection to the community.

In the laboratory it has been found that these sand-flies must be bred

three months of the year in Bengal and Assam but does not in other provinces, this may account for both the geographical distribution and the seasonal incidence of kala-azar in India.

**Correlation of sand flies and kala azar**—So far as India is concerned every epidemiological observation fits in with the sand fly hypothesis of transmission. Further, this sand-fly has actually been found in large numbers in every locality where kala-azar occurs, it is a persistent human blood feeder, a large percentage of the flies that feed on an infected person acquire the infection, infected flies have been found repeatedly in nature, this is not true of other sand-flies, which are more prevalent in the non-endemic areas, nor of insects of any other genus so far experimented with, in this fly an anterior development of the flagellate infection occurs and is unlikely to be purposeless (in natural flagellate infections which pass from insect to insect the development is usually posterior), and it has been shown experimentally that the fly is capable of transmitting the infection to man and other mammalian hosts by its bite (see p 144). All these facts make it almost certain that this insect is the most important agent in the natural transmission of the disease from man to man in most localities, although it may not be the only agent.

**Sources of infection**—It is believed that in India man is the sole naturally, during an attack sent in the peripheral blood, it has been shown that the

post-kala-azar dermal lesions will also provide the flagellate infection. Further, it has been shown (Napier *et al.*, 1933) that a patient treated and cured (of the visceral infection) may still be a source of infection to a sand-fly. In such a case the blood culture is negative, so that infection must take place from the parasites that are lying dormant in the skin—the

causes of the later dermal lesions. It is thus easy to understand how infection once established in a locality remains endemic.

has been reported from Assam

### IMMUNOLOGY

**Antigenic properties**—Noguchi demonstrated that there were differences in the antigenic structure between *L. donovani*, *L. tropica* and *L. brasiliensis* but that *L. infantum* was antigenically identical with *L. donovani*. There are strains of *L. canis* (of the dog) that are closely related to *L. donovani* and others that are related to *L. tropica*.

It is usually stated that no agglutinins are present in the blood in kala azar but new methods have demonstrated specific agglutinins both flagellar and somatic in infected and immunized experimental animals.

The presence of a specific complement fixing antibody was demonstrated by Hindle *et al.* (1926) they used a flagellate emulsion as antigen.

**Immunity**—There is evidence of some natural immunity to infection. It has been shown that healthy adult man is not always susceptible. The injection of infected material have not produced the disease (these volunteers) and two accidental self

inoculations by the writer in which no infections occurred and five

are immune to infection with *L. canis*. There is however no cross immunity against other leishmanial infections e.g. *L. tropica* which causes oriental sore.

**Secondary factors determining infection**—Many observations make it seem probable that some secondary factor determines the onset of the disease in a person inoculated with the parasite. It has been pointed out that the worst outbreaks in Assam were associated with conditions of as the malaria epidemic determined the original 1917 which preceded the

On the other hand there is little reason to suppose that general lowering of resistance is an essential preliminary to kala azar infection as weak and debilitated people are not usually picked out, but the writer has suggested that possibly certain specific infections might prepare the way for a general visceral invasion of the parasite in a person in whom it had been lying dormant for some time (the incubation period varies from a few weeks to a year or more) and we have produced epidemiological, serological and cytological evidence suggesting that malaria and

enteric were two such infections, part of the evidence for the inclusion of the latter disease was that in Calcutta a large percentage of the patients diagnosed serologically or bacteriologically as enteric fever and coming from parts of the city where kala-azar was endemic subsequently returned to hospital with kala-azar

### PATHOLOGY

**Morbid anatomy and histopathology**—Parasites are found in all parts of the body, particularly in tissues rich in cells of the reticulo-endothelial system. The body to invasion appears to be a macrophages, the cells of this system undergo proliferation actually precedes parasitization, as often the cells in the centre of an island of histiocytic tissue will not be parasitized, whereas those at the periphery are heavily so. Nearly all the histological changes observed in the

The spleen is almost always enlarged, it may be immense, weighing as much as ten pounds in an adult. The capsule is usually thickened and occasionally at the site of recent perisplenitis there is considerable thickening. Its consistence is variable, but in most cases it is soft and pulpy, the surface bulging on section of the capsule. In the more chronic cases it is firm, retaining its shape on removal from the body but it is usually very friable and is seldom hard and fibrous like the chronic malarial spleen. The cut surface has a uniform dark red appearance, if the knife is drawn across the cut surface of the soft type of spleen, quantities of pulp will be scraped off, and the surface will be felt to be quite smooth. There may be infarcts.

Microscopically, there is infiltration by masses of heavily parasitized macrophages, these encroach on the lymphatic follicles (Malpighian corpuscles), which eventually disappear almost completely. There is considerable enlargement of the vascular spaces. The large parasitized macrophages appear to dominate the whole picture.

The liver is usually enlarged. It is firm, retaining its shape well on removal from the body. It is friable, but not so friable as the spleen. The capsule is thickened in places and the liver on section shows the greasy appearance associated with fatty degeneration. It also shows the nutmeg

appearance of the chronic cell congested liver. The cells affected are the reticulo-endothelial cells and parasitized so much that they become chrysa cells, which some writers consider later stages of the infection. The disease in the portal zone and in some reticulo-endothelial cells will be seen in the portal zone. The tissue invades the lobules and in the portal zone the capillaries are dilated. The liver cells may be atrophied and the parenchyma cells. Later this is partially superseded by fibrous tissue producing the interlobular cirrhosis that occurs in the later stages of the disease.

..

bone marrow red  
there is a considerable  
argely displaced by

proliferating and parasitized macrophages these may occupy almost the whole marrow space but there are usually a few areas of hæmopoietic activity

In other organs and tissues the changes are inconstant and the reports of observers in different countries vary

At the same time the changes in the skin are also inconstant and the reports of observers in different countries vary

The changes in the intestinal tract which have been reported from

#### intestinal tract

The histopathological findings in the skin are somewhat anomalous  
 Workers in the skin of a large  
 percent of the skin of a large  
 failed to find any dermal lesions (vide  
 infra) but it is rarely reported  
 in China that kala azar too the  
 parasites in the nail numbers that it  
 is not possible to demonstrate them

Ch the zona fasciculata  
 and zona commonly but not  
 constant been comparatively  
 rarely

**Post kala azar dermal leishmaniasis**—When the visceral infection has been overcome either spontaneously or with the aid of treatment some of the parasites in the skin may survive and continue to multiply very slowly taking a year or more to produce clinical lesions. In the early hypopigmented lesion of post kala azar dermal leishmaniasis the epidermis has undergone very little change but there is some decrease in the pigment in the cells of the basal layer. The sub papillary layer is oedematous and the vessels are large and dilated the latter change being very marked in cases with erythematous lesions. There is some infiltration by macrophages in the deeper layers around the sub papillary plexus. Parasites are scarce in these early lesions but can be demonstrated by cultural methods and sand flies allowed to feed on these areas become infected. As blood cultures are usually negative at this stage the sand flies must obtain the parasites from the local tissues

In the nodular lesions the epidermis is thinned down to a few layers of cells and the papillae are flattened out. Below in the reticular layer there is much proliferation of the macrophages which form into large masses of cells many of which are parasitized

**Blood picture**—The most characteristic changes in the blood picture are the leucopenia and the decrease in granulocytes. Some degree of anaemia is always present, except possibly in the earliest stages. The red

The decrease in leucocytes occurs early in the disease, and is a useful diagnostic sign. In 80 per cent of well-developed cases the count is below 4,000 per c mm (see figure 30)

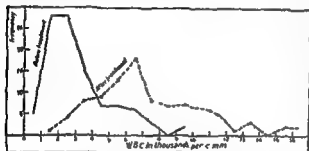


Figure 30 The leucocyte count before and after treatment frequency curves based on 100 cases

are often absent and are usually not more than 1 to 2 per cent of the low total count, this diminution is less noticeable among Europeans in whom the normal eosinophil count is about 2 per cent, but among Indians it is higher, indeed 7 to 10 per cent cannot be considered abnormal among some Indian populations.

There is sometimes an absolute increase of large mononuclear cells and there is always a relative increase, it has been shown by supravital staining methods that two-thirds of these cells are histiocytes. In the lymphocytes there may be a slight absolute decrease, but there is nearly always a definite relative increase. There is usually a marked shift to the left in the Arneeth count the mean Arneeth index in thirty cases being 92.

There is nearly always a reduction in the number of platelets the count being usually about 200,000 per c mm.

The indirect van den Bergh reaction is nearly always positive, the quantitative test usually shows from 1 to 3 mg of bilirubin per 100 c cm.

The erythrocyte sedimentation rate (ESR) is very much increased, more consistently so than in any other disease (Napier and Henderson, 1931). The mean reading (Westergren) in 77 mixed cases recently examined was  $68.3 \pm 11.2$  mm, only in one case was the ESR below 40 mm.

Hydrogen ion concentration of the blood in kala-azar the alkaline reserve is reduced. The true change is a reduction

\* Though the writer's personal experience of kala azar during the last 20 years amounts to more than ten thousand cases he has only had one case of complete agranulocytosis under his charge (Das Gupta and Sen Gupta 1943).

The calcium content is reduced it is usually below 9 milligrammes per 100 c cm. The blood sugar is reduced and is sometimes as low as 0.05 per cent. The laevulose tolerance is also reduced.

on this increase in the euglobulin which is often very considerable in advanced cases

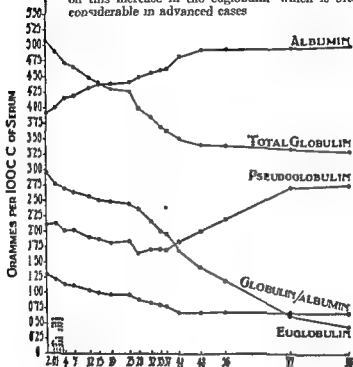


Figure 31 The proportions of the serum proteins before and after treatment the latter is about normal

the moder  
imentation  
liver dys

**Urine** — There is nearly always a trace of albumin and marked increase in urobilin. Otherwise there is no characteristic change the urine is often concentrated and has the usual characters of a febrile urine during febrile periods.

## SYMPTOMATOLOGY

Incubation period—There is very little exact information about the incubation period of this virus. It is probably between 1 and 2 weeks.



a kala-azar case suggestive symptoms appeared after a few days of each of  
by sand  
months  
considered to be from two to four months

A case of congenital infection has been reported

**Onset**—The nature of the onset is not constant, it is sometimes acute, but in many cases it is extremely insidious. In India, the cases can be classed, as far as the onset is concerned, into three groups: the enteric-like, the malaria-like, and the insidious type.

In the enteric-like type the patient suffers from general malaise without any localizing symptoms, and the temperature climbs rapidly, reaching 103° or 104°F in about a week, this is maintained for a week or so at a high continuous or a high remittent temperature, and then the temperature gradually falls to 99°F or even to normal. Usually abdominal symptoms are absent, the spleen is sometimes just palpable but not tender, the liver is not usually enlarged. The attack may simulate one of enteric fevers very closely, but the distinguishing features are a pulse-rate of about 120 a minute and the absence of the typical coated tongue and of the characteristic toxic drowsiness of the enteric patient.

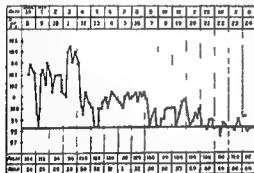


Figure 32 Temperature at onset of kala-azar

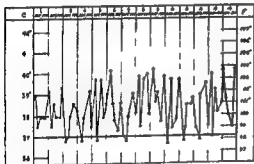


Figure 33 Chart showing double rise of temperature in 24 hours

The temperature may remain low for a week or so, then it will gradually creep up again. In this second febrile attack the temperature is more likely to be remittent or even intermittent, and the classical double rise in the twenty-four hours may appear (see figure 33). Meanwhile the spleen will have enlarged and should be definitely palpable by now. This attack may be diagnosed as an enteric fever relapse but by the time that a third bout occurs there is little excuse for this mistake.

In the malaria like type the onset is sharper, and the fever may be

as it usually does in malaria

In the insidious type, the patient cannot give a clear history of the time of onset of the illness but often states that for some months he has not felt well, and possibly he has had attacks of irregular fever. Eventually he

comes to hospital because of the size of his spleen or because of some complication such as dysentery or pneumonia and it is obvious from the advanced state of the infection indicated by the serum test that he has been suffering for at least six months

A modification of this is the truly asymptomatic type where the patient's condition is discovered accidentally when for example he happens to bring another patient to hospital

**Transient infection**—In a few cases with the febrile type of onset the infection has been transient the parasite has been demonstrated by blood culture but meanwhile all the symptoms have subsided and specific treatment has not been given The writer traced a few cases of this kind in which symptoms did not return for three or four years at least the

which treatment was given

### Signs and symptoms of the established disease

Unless otherwise stated the following description will apply to a patient

**Symptoms**—When the disease has reached a comparatively advanced stage the patient complains of fever progressive loss of weight weakness increasing darkening of the skin—usually noticed by his friends—falling of the hair palpitations and dyspnoea intermittent attacks of diarrhoea bleeding from the nose and from the gums and a persistent and very irritating cough Headaches which would be expected with the fever are noticeably absent in most cases and the appetite is good and sometimes ravenous The patient will also usually complain of progressive enlargement of the spleen in some cases this is the first symptom in others the enlargement is not noted for a month or two after the onset of the fever

**General appearance**—The patient may be emaciated but is often moderately well nourished the hair is dry lustreless and sparse the natural pigmentation of the skin of the forehead of the temples and around the mouth in dark skinned people is intensified and contrasts with the blood

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of the second, two inches at the end of the third, and so on, there are, however, exceptions to this general rule. There is practically no condition in which so rapid an enlargement of the spleen can take place, from being just palpable. The spleen will sometimes reach the level of the umbilicus in a month. On the other hand, there are cases in which the enlargement is slow or checked by the intervention of some inflammatory complication, such as broncho-pneumonia or cancerum oris.

The actual size of the spleen is not a very useful diagnostic point, although the regularity and comparative rapidity of the enlargement may arouse suspicion.

The peculiar soft doughy consistence of a kala-azar spleen, however, is highly significant, it is not common in other conditions, whereas the wood-like resistance of an old-standing chronic malarial spleen is uncommon. In even a chronic case of kala-azar 'The more chronic the disease the harder the spleen' may be taken as a general rule.

**Liver** — There is nearly always some degree of enlargement of the liver. An enlarged soft liver, with a thinned-out edge, overlapping a large soft spleen is very characteristic of the disease. Some tenderness is sometimes present but is in no way comparable to the tenderness associated with acute hepatitis or liver abscess. Occasionally, hepatic enlargement appears to take the place of splenic enlargement, but usually both conditions are present and there is little evidence that this enlargement is in any way compensatory, the liver is enlarged in at least 80 per cent of all cases of kala azar, and in those cases in which there is no splenic enlargement the liver is on the whole less often enlarged.

**Jaundice** is not common in the early stages of the disease, but later it may occur and is a bad prognostic sign.

words continuous, remittent, and intermittent, and interposed the words 'double' and 'triple' wherever suitable. There is, however, one form of fever which, when it occurs, is characteristic of the disease, i.e. the double intermittent or remittent fever, the temperature subsides towards early morning and remains low until about midday, it rises in the afternoon, subsiding again towards evening, about eight or nine o'clock at night it again rises, or the second rise may be delayed until midnight, and again it subsides towards morning. In order to demonstrate this double rise it may be necessary to take the temperature every three hours, day and night.

### PLATE III

- Fig 1 A group of kala-azar patients attending a village treatment centre near Calcutta. Note predominance of children and that some are well nourished.
- Fig 2 Kala-azar in Indian child typical case.
- Fig 3 Kala-azar in Chinese child with commencing cancerum oris on right side (Courtesy of Dr E C Faust).

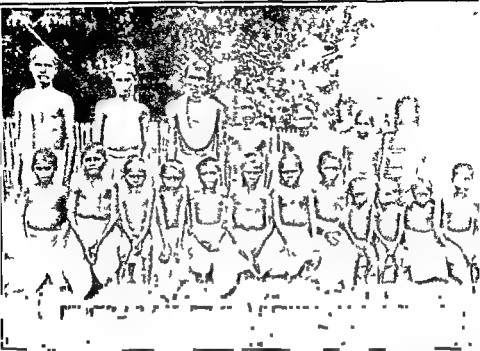


Fig 1



Fig 3

Bleeding from the gums and epistaxis generally occur. Purpuric spots are not very uncommon and are sometimes a terminal symptom in a case running an acute course, they are often associated with uncontrollable hæmorrhage from the gums and into the bowel, a condition suggestive of Henoch's purpura. Retinal hæmorrhages have been observed in a few cases.

**Alimentary tract**—Gingivitis, with subsequent loosening of the teeth is common. Stomatitis, other than cancrum oris, is not very uncommon at any stage, and in the late stages cancrum oris is the most fatal complication. It is not seen so often when a parenteral treatment was introduced, but is far commoner than

The appetite is nearly always good, but the digestion is usually less satisfactory, with the result that intestinal disturbances may result from indiscretions in diet. Fractional gastric analyses show that there is little departure from the normal in the gastric acidity.

Diarrhœa and dysentery are such common complications that it has been suggested that there is a specific leishmanial dysentery, there is no support for this suggestion. Bowel disturbances are comparatively rare in a well-regulated hospital, and respiratory diseases are far more common complications in these circumstances, in the country districts the reverse is usually the case. A terminal dysentery sometimes occurs.

**Respiratory system**—The respiratory system is peculiarly prone to inflammatory processes. Ataxic pneumonia is usually present without any account for it. In a few cases pleurisy occurs, seriously interfering with respiration. It is suggested that this is due to irritation of the vagus from pressure caused by the enlarged spleen. In the later stages, some congestion of the bases of the lungs is common. Broncho-pneumonia is a very common complication.

The nervous system seems peculiarly free from attack by the parasites or their toxins. The mental condition is always quite clear, even in the final stages, and delirium is less common during pyrexial attacks in this disease than in any other, a point of diagnostic value.

Herpes zoster occurs sometimes during the course of the disease in a patient who is not under treatment, but it is much more often seen in a patient receiving antimony injections.

**Skin and subcutaneous tissues**—Certain very prominent changes, probably of a trophic nature, take place in the skin of a kala azar patient.

(1) The whole skin surface becomes dry, rough, and harsh. The hair falls out and becomes very thin, sometimes children become almost bald.

any special liability of the tissues to attack by these organisms. Among some peoples in India it is the custom never to allow a patient with fever to have a bath.



clean tongue and the mental alertness of the patient will be helpful signs. At this stage the leucocyte count will usually be about 4,000 per cmm. The serum tests will not be very helpful. The aldehyde test may be negative, but the experienced will often detect a faint cloud which should

#### THIS STAGE

In the later stages (five months), the points of diagnostic value are the history of a long-continued fever resistant to quinine, progressive enlargement of the spleen, loss of weight, epistaxis or bleeding from the gums, falling of the hair, and increasing darkness of complexion (in dark-skinned people). Additional physical signs will be the spongy consistence of the enlarged spleen, the enlargement of the liver, the pulsation of the carotids in the neck, the clean tongue, and the rapid pulse.

Leucopenia will now be established, and the leucocyte count will almost certainly be below 4,000 and possibly as low as 2,000 per cmm, eosinophils will be few or absent, and granulocytes will form less than 50 per cent in the differential count, and the red cells will number about 3,000,000 and will be slightly hyperchromic. The aldehyde test will now be strongly positive. If it is desirable to confirm the diagnosis, after failure to find the parasite in the peripheral blood, puncture of the lymphatic glands, sternum, or spleen is the easiest method at this stage.

It should be remembered that every sign and symptom of the disease may be absent, the writer has seen many cases that were afebrile for months at a time, if not throughout the disease, and many in which the spleen was not palpable.

**Therapeutic tests**—It may be justifiable to exclude other infections, such as malaria, by giving quinine, but it is never justifiable to give a few antimony injections to exclude kala-azar.

If other conditions that require immediate action can be excluded, it is far better to await developments than to rush into a diagnosis of kala-azar. Once treatment is begun, diagnosis becomes far more difficult. Patients do not die in the early stages of the disease (in India, at least) and, although their temperatures may run very high, they do not suffer much discomfort. There is no truth in the oft-repeated statement that the prognosis is better if the treatment is undertaken early, on the contrary, the best results are obtained in cases in which there is a history of four or more relapses. The treatment should be continued until the patient has had a full course of treatment and has had a full recovery of resistance.

In special circumstances it may be justifiable to make a provisional diagnosis of kala-azar and to give a full course of treatment, but once the treatment has been started failure to effect an early improvement must not be allowed to discourage one. Many resistant cases of kala-azar give a history of therapeutic tests and tinkering treatment of this kind.

#### Diagnostic methods

Parasites in peripheral blood on the persistence of four films made

present in the depends searching y Wright

for the opsonic index and stained by Leshman's or Giemsa's method it should be possible to establish a diagnosis in 60 to 70 per cent of cases. Casual examination of an ordinary blood smear is of little value.

Blood culture should produce a positive result in 100 per cent of cases.

agar slope with condensation fluid), these tubes are kept at 22°C and a drop of the condensation fluid is examined at intervals in the fresh state. The flagellates will be seen as actively moving forms among the red cells. As the medium is easily contaminated it is advisable to sow into at least three tubes.

**Sternum puncture**—Recent experience has shown that this is a very valuable method of diagnosis. In a recent series of 80 subsequently proven cases of kala azar parasites were found in the sternum puncture smear in 71, or 89 per cent. In six of nine cases in which no parasites were found a

additional method and one that can be employed when the spleen is not puncturable it has not replaced spleen puncture. It is a more painful procedure and though probably safer experience has still to prove this.

A culture on NNN medium can be made from the material obtained by sternum puncture but it is difficult with the apparatus at present at our disposal to avoid contamination. Satisfactory cultures will however always show leishmaniae in a case of kala azar.

**Technique of sternum puncture**—The Salah needle used for sternum puncture is shown below (figure 34). It is made of rustless steel and the bore is about the

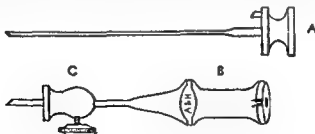


Figure 34 Sternum puncture needle (actual size)



**Procedure**—The hair over the sternum, if there is any, is first clipped with a pair of scissors, shaved with a razor, and the skin finally cleaned thoroughly with alcohol. The best site for the puncture is just to one side of the middle line at the level of the second intercostal space. This area is first anesthetized by infiltration with a 2 per-cent solution of novocaine, or its substitute. Some solution is first injected into the skin with a fine needle attached to a 2-cm syringe, then the needle is pushed down to the periosteum and the rest of the solution injected. About 1 cm is usually sufficient in a thin individual, but more is required where the subcutaneous tissue is deeper. After an interval of 5 to 10 minutes, the actual puncture is made.

The apparatus is held with the knob of the stylet in the palm of the hand and the guard is are pie of the cavity the spi sterilize and the a drag or not. Only a few drops of marrow (sinusoidal) blood are removed and the syringe and the sternum-puncture needle are withdrawn, digital pressure is applied over the puncture for a minute or two and the puncture is sealed with collodion. With the needle still attached to the syringe one drop is placed into NNN medium and the rest placed on clean slides for smears to be made; these are stained with Leishman's or Giemsa's stain and examined in the usual way.

Only very rarely will one fail to obtain blood. The commonest error is to fail to allow a sufficient length of needle. In this case the guard must be adjusted slightly, the stylet replaced and the needle pushed in a little deeper. Occasionally the needle goes too deeply and has to be withdrawn slightly before blood will come.

**Tibia puncture.**—This is useful in small children, up to the age of about two years especially as in these young children the sternum is very soft, and undressed will not usually support the needle while the stylet is removed. The percentage of positive findings is however smaller.

The puncture is made about the middle of the shaft of the tibia with a sternum-puncture needle. More force is required as the bone is denser even than the sternum of an adult.

**Spleen puncture**—The dangers of spleen puncture are much exaggerated, but nevertheless it should never be performed unnecessarily or carelessly, and the adoption of a rigid technique is advisable. In 95 per cent of cases of kala-azar the parasites will be found in large numbers in the smear (stained by Leishman's or Giemsa's method) and in every case by cultivation directly into NNN or Senekjiev's medium.

#### Technique of spleen puncture

**Preparation of patient**—If possible the patient is given a dose of calcium lactate 30 grains on the previous night another dose in the morning and a third dose immediately after the operation. The patient is given no food on the morning of the operation, and is kept in bed for the day, he is allowed food one hour after the puncture.

The writer has followed this procedure whenever possible for over 20 years and he has had no disasters in over 7000 spleen punctures, he therefore hesitates to abandon it, though he is doubtful if it is necessary, or even if the rationale is sound. In the out-patient department he has used a considerably modified procedure, reducing the calcium lactate to two doses and the resting time to one hour after the puncture, with equally good results.

**Procedure**—The puncture is done with a 5-cm syringe and a no. 11\* needle about 1 to 1½ inches. The attachment should be used.

\* No. 19 in the

correspondingly decrease the danger, it is not essential (figure 35) The syringe is oil-sterilized or if an all glass syringe is used it may be dry-sterilized

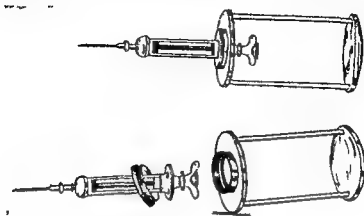


Figure 35 Spleen puncture fitment for syringe

The patient lies on a flat bed with fracture boards if necessary, without a pillow and the operator sits on the edge of the bed on the left of the patient. The splenic area is sterilized with alcohol. The spot chosen for the puncture is half an inch below the costal margin about the centre of the parietal surface of the spleen at this spot the skin is touched with pure phenol which after a minute is wiped off with a spirit swab. If an ordinary syringe is used an assistant standing on the other side of the bed should place his right hand below the spleen to prevent downward movement if the special spleen puncture attachment is used the operator's left hand is free and he can do this himself.

The puncture is made in two movements. By the first the skin alone is

in the needle and not on any account must the withdrawal of the plunger be continued because blood cannot be seen in the syringe. Sometimes the syringe does fill rapidly with blood but this is not a serious matter.

A binder should be put round the abdomen with a pad over the point where the puncture was made. In about 10 per cent of cases the spleen is tender for the next 24 hours but most patients do not have any discomfort.

indicated

In at least 10 per cent of kala azar cases parasites will not be found in the smears although culture will probably give 100 per cent positive results. It is usually necessary to make the puncture between the ribs, and also to withdraw the plunger a number of times to be certain of obtaining blood from the organ as not so vascular as the spleen. Otherwise there is little difference in the technique.

**Gland puncture**—In China (Cochrane, 1912) and in the Sudan (Kirk and Sati, 1940) gland puncture is found a useful method of diagnosis, in the latter workers' experience, a diagnosis can always be made by this method, but other workers in the Sudan have been less successful. In India, we seldom find the lymphatic glands sufficiently enlarged for the puncture to be made, and when, in an emaciated patient, it is possible to grip the glands between the finger and thumb, the findings are usually negative.

**Procedure**—Take a medium-sized dry sterilized hypodermic needle (no 11). Grip a lymphatic gland *eg* an inguinal or a cervical gland between the finger and thumb and after sterilizing the skin plunge the needle into the gland and leave it for half a minute or so. Then withdraw it and force out the contained way, scanty leishmanias. It is usually possible to obtain enough fluid with

**Culture on laboratory medium**—The material obtained by spleen, sternum, liver, or gland puncture may be inoculated into NNN or Senekje's medium. This must be done with very strict aseptic precautions.

After the spleen puncture has been made the material should first be

earlier date. Great care must be taken to prevent contamination when a tube is opened. A loop of condensation fluid is examined under the high power objective and, if it is positive, rapidly moving leptomonad forms will be seen darting across the field.

**Senekje's medium**—In 1000 ccm of distilled water dissolve 50 grammes of 'bacto' beef extract. Heat at 50° C for one hour and at 80° C for 5 minutes. Filter through paper and add—Neopeptone (Difco), 20 grammes, Agar (preferably Nobel), 20 grammes, Sodium chloride, 5 grammes.

Adjust to pH 7.2 to 7.4 and autoclave at 15 pounds pressure for 20 minutes.

As the agar cools, but before it 'sets', add 10 per cent of defibrinated rabbit's blood. Mix by rotating between the palms and slope or pour into a petri dish.

#### Serum tests

The serum tests all depend on the increase in the euglobulin fraction (*vide supra*). Many modifications have been introduced, but the writer much prefers the aldehyde test. Chopra's antimony test has the advantage of giving a positive result earlier in the disease, but in cases with a large spleen not due to kala-azar it is liable to give a false positive, therefore, in an early case without splenic enlargement, both tests should be done, but in a well established case with a large spleen, the aldehyde test can be relied upon.

**Aldehyde (Naper) test**—This reaction is not fully developed until the third to the fifth month and after successful treatment takes about four months. *test for cure*

two drops of commercial formalin are added to the serum. The serum becomes solid and completely opaque within a very few minutes if it is positive. Doubtful results are solidification of the serum with various degrees of cloudiness. In a negative result the serum remains crystal clear, although it may solidify

**Reading the result**—The final result should be read at the end of 24 hours, but with experience a very good idea of the probable result will be obtained in half an hour

(a) **Positive** Solid, white and completely opaque (hard-boiled egg), no light transmitted through the serum If complete opacity is produced in 20 minutes, the result is +++, if in two hours ++, and if in 24 hours, +

(c) **Doubtful** ± Solid, slightly milky but quite transparent after 24 hours

(d) **Negative** (—) Solid but crystal clear after 24 hours

(e) **Negative** —ive Serum unchanged (fluid), after 24 hours

**Diagnostic value of test**—The test is seldom completely negative after one month from the onset of the disease and after five months it is nearly always

negative diagnosis can be made in a patient with a long history of illness and a spleen b uld  
certainly ful  
result w ort  
history

TABLE II THE INTERPRETATION OF THE RESULTS OF THE ALDEHYDE TEST

Aldehyde test reading Size of spleen	+++ ++ or +*	(+)	±	(—)	—ive
Below the navel	Kala azar	Doubtful	Not kala-azar	Not kala-azar	Not kala-azar
Four inches or more below costal margin but not below the navel	Kala azar	Probably kala azar*	Possibly kala azar	Probably not kala-azar	Not kala-azar
Two inches or more but less than four below costal margin	Kala azar	Kala azar*	Possibly kala-azar	Probably not kala azar	Doubtful
Palpable but less than two inches below costal margin or not palpable	Kala azar	Kala azar*	Possibly kala azar	Doubtful	Doubtful

\* Except when there are obvious signs of advanced tuberculosis or leprosy

**Antimony (Chopra) test**—The serum is diluted ten times with double distilled water and is placed in a narrow bored test tube, to this, 4 per cent

**Reading the result Positive** This is indicated by a heavy flocculent precipitate forming almost immediately, this settles as a flocculent mass in the course of half an hour or so

**Doubtful** This is indicated by a fine granular precipitate which settles more slowly but forms a more compact mass at the bottom of the tube

**Negative** In a negative result no precipitate occurs

There is usually a doubtful reaction at the end of the first month or even earlier and a positive one at the end of the second or third month. In cases of enlarged spleen from other causes, a positive reaction in some times given, therefore the test can be relied on only in cases with little splenic enlargement

TABLE III THE INTERPRETATION OF THE RESULTS OF THE ANTIMONY TEST

Antimony test reading	Positive	Doubtful	Negative
Size of spleen			
Below the navel	Doubtful	Not kala-azar	Not kala-azar
Four inches or more below costal margin but not below the navel	Probably kala azar	Doubtful	Not kala azar
Two inches or more but less than four below costal margin	Kala azar*	Doubtful	Probably not kala azar
Palpable but less than two inches below costal margin or not palpable	Kala azar*	Doubtful	Doubtful

\* Except when there are obvious signs of advanced tuberculosis or leprosy

**The Globulin-precipitation test**—In the globulin precipitation test one part of serum is added to three parts of distilled water. In kala azar a flocculent precipitate forms. The test has the same limitations as the above two tests and is less specific

**Other experience**—In the Sudan the serum tests have not proved of much value, and in China the more delicate tests which give very misleading results in India e.g. the globulin precipitation test are sometimes preferred to the aldehyde test. A recent elaboration is a photometric test with 1 in 1000 dilution of serum and 1 in 100 urea stibamine solution (d Oelsnitz 1938)

est with a flagellate culture disease is well established (Grevil Sen Gupta & nunciation) has devised a ith infected animals

**Diagnosis**—In the early stages, kala azar has to be distinguished specially malaria typhoid fever and distinctive exanthemata or localiz

- (a) other febrile diseases especially those in which there are long febrile periods alternating with periods of apyrexia
- (b) conditions in which the spleen is enlarged
- (c) conditions in which the liver is enlarged
- (d) conditions in which there is marked leucopenia

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fever  
the

cirrhosis schistosomiasis and histoplasmosis. In none of these instances will differentiation present any difficulties if the above procedures are followed.

**Diagnosis of post kala azar dermal leishmaniasis**—The hypopigmented macules and the erythematous rash are clinically very typical and will seldom be mistaken by those with experience of the disease. In these cases parasites can be found in the tissues but it is difficult to demonstrate them and there is no simple procedure which can be recommended for routine use. On the other hand in the nodules the parasites can be detected with ease: a nodule is seized with a fine pair of forceps and by rubbing Leishman's endothelial

### PREVENTION

A sufficiently large number of facts regarding the epidemiology of the disease has been accumulated for us to recognize the conditions under which transmission occurs and the first measure of prevention is to avoid these: the reader is referred back to pages 139-142.

For transmission to occur two factors are necessary: (a) the source of infection and (b) the transmitting insects and preventive measures can be considered under these two headings.

(a) **The source of infection**—There are in India, as far as we know, no animal reservoirs of infection so that man is always the source of infection. A patient with kala azar will be the richest source of infection but once treatment has been started the parasites usually disappear from the peripheral blood.

The only control measure that has been undertaken on a public health scale has been a treatment campaign. Such a scheme was instituted in Assam from the year 1922 on. In Aomlancham, where there was a high incidence in Bengal a few years later, it had a great influence in controlling the disease.

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incidence in the last year or so, no similar rise is yet (1942) apparent in the other two provinces.

In a small experimental area near Calcutta where we undertook an intensive treatment campaign about 15 years ago there has been no recrudescence of the disease. In an area where there were 121 and 137 cases in the years 1925 and 1926 there were no cases in 1937 and only sporadic cases have occurred since.

As a case of dermal leishmaniasis is a potential source of danger and there are always residual cases of this condition in an endemic area it will probably never be possible to eradicate kala azar completely by

means of treatment campaigns, but the disease can apparently be controlled to a great extent, by reducing the sources of infection to a minimum.

In the Mediterranean endemic areas and in China, the evidence is accumulating that dogs act as reservoirs of infection. An attempt should be made to estimate the extent of the infection amongst the local canine community, and, if it is found to be high, a campaign against all stray dogs should be undertaken.

(b) The transmitting insects—The conditions under which sand flies (*Phlebotomus argentipes*) flourish have been indicated (p. 145).

Dark, damp, and stagnant places should be avoided, no dark corners paved with cement and no crevices should be allowed, and chloride of lime should be used on the earth near the house to destroy the flies. Roofs should be of brick and should be kept in repair. In the case of poorer-class dwellings, it is better to have them repaired with bamboo-matting walls than mud walls or even plastered reeds.

The control of sand-flies in rural areas is very difficult and has yet not become a practicable measure for preventing kala-azar, but the removal of a coolie colony to a new site was practised even before the means of transmission was understood, and the measure proved very successful. By this means the old breeding places of the sand-flies were left behind and the flies on the new site. It was simply burnt down and re-erected, thus breaking the cycle of the kala-azar epidemic.

### TREATMENT

**Historical**—The history of the treatment of kala-azar can conveniently be divided into three phases: the pre-antimony period, the antimony era, and the new chemotherapeutic era.

**The Pre-antimony Period**—Prior to 1915 kala-azar was, it is said, fatal in 80 per cent of cases. It disappeared spontaneously more often than was previously the case with the disease within a few days.

**The Antimony Era**—In 1915 Di Cristina and Caronia introduced the treatment by potassium antimonyl tartrate given intravenously, a treatment which had been used two years earlier by Vianna and Machado in American mucocutaneous leishmaniasis. This treatment was used in India by Rogers and by Muir later in the same year, later the former introduced a valuable modification using the less toxic sodium antimonyl tartrate.

In China and the Sudan on the other hand the result obtained with the antimonyl tartrates was so poor that these drugs were never used systematically.

The next important advance was the introduction of the pentavalent antimony compounds. All the earliest and most of the more successful of these have been prepared by Professor Hans Schmidt. Caronia first used sodium para-acetylaminophenyl stibamate clinically in Italy in 1916. After the 1914/18 war when the preparation of this compound was abandoned, it was written up by the writer in 1923 and was used in India (1923) and successively in the world. The beginning of the world stibamine prepared in the treatment of kala-azar was in the treatment of Peter.

In 1937, Napier Chaudhuri and Rai Chaudhuri first used solustibosan, Bayer 561 a pentavalent compound that can be given intramuscularly and makes a stable solution, so that it can be supplied conveniently in ampoules in our later experience we found it less efficacious than neostibosan

we used 4 4'-diamidino-diphenoxy pentane and Kirk and Sati (10) in 8 cases of followed this were antimony- g was the most

Kirk has also given a short trial to 4 4'-diamidino-diphenoxy pentane and our results so far with this drug have been very satisfactory In some twenty odd cases we have obtained an earlier fall of temperature than with the diamidino-stilbene the fall of blood pressure appears to be less but we cannot yet say whether the neuropathy will follow the injections of this preparation also

Discussion — As far as India was concerned, the introduction of the h rate among out the treat patients were

The advantage of the pentavalent compounds is that they are very much less toxic and can therefore be given in very much larger doses this means that the duration of treatment can be cut down very materially They do not cause some of the serious by effects of the antimonyl tartrates, and consequently the mortality among patients under treatment is very much lower, in our series of more than 500 cases treated by neostibosan, it was only about 2 per cent By an intensive course of treatment the period in hospital can be reduced to one week

per cent more 934, and came t was required ewhere in the e as much the Sudan 10 per cent, treatment was prolonged

The aromatic diamidines appear to constitute another advance, as infinitely better results than hitherto have been obtained in the Sudan, and even in Calcutta our previously more successful results have been surpassed, further, excellent results have been obtained in antimony-resistant cases



### Specific treatment

**Antimonyl tartrates** —The only reason for using the old form of treatment with the antimonyl tartrates is the higher cost of the new preparations. Relatively unsatisfactory as the former salts are, they are better than no treatment at all, and in poor countries will probably remain in use for many years.

Either the potassium or the sodium salt may be used, but the latter is less toxic. A 2 per-cent solution in physiological saline (0.85 per cent in distilled water) is prepared, and to it 0.5 per cent of phenol is added to prevent the growth of moulds. This solution will keep for some weeks but it should be examined carefully before it is used to see that there is no precipitate. For adults the initial dose is 2 ccm, this should be increased by 1 ccm with each dose up to 5 ccm, the injections must be given intravenously, and if the solution leaks into the tissues very severe reactions will follow, injections should be given on alternate days or three times a week, and, as a minimum twenty-five injections will be necessary.

Coughing, vomiting, and joint pains are common accompaniments of this treatment, and it may be necessary to increase the dosage more slowly or even in some cases to reduce it so as to obviate these symptoms, this prolongs the course of treatment and the results are correspondingly less satisfactory.

**Neostibosan** \* . di-ethyl amine *para*-amino-phenyl stibinate —This is supplied in sealed ampoules as a light-brown powder, which is dissolved in sterilized distilled water. The strength of the solution is not a matter of great importance but we generally use 5 per cent for intravenous injections although strengths up to 25 per cent can be used.

In adults it is better to give the drug intravenously, but in children this is often difficult, it can be given intramuscularly, and then a 25 per cent solution should be used, this reduces the bulk of fluid and makes an isotonic solution. It should be given into the buttocks on alternate sides there may be slight local reaction but often there is none and abscess formation is very rare. Only one abscess occurred in a series of twenty adults treated with intramuscular injections, and we have never seen an abscess in a child.

**Dosage** —The first dose for an adult should be 0.2 and subsequent doses 0.3 gramme. The adult dose can be given to children of 60 pounds or more, about 50 pounds 0.25 gramme, about 40 pounds 0.2 gramme, about 30 pounds 0.15 gramme and about 20 pounds 0.1 gramme for the maximum dose may be taken as a rough guide to dosage. Children tolerate a relatively larger dose than adults and seem to require it. It may be advisable to modify the dosage in very debilitated patients.

The injections may be given daily or on alternate days, better results being obtained from daily injections.

**Length of treatment** —It is extremely difficult to be dogmatic about the length of the course of treatment. A high rate of cures was obtained by giving eight injections on eight consecutive days. Workers in other

\* Di-ethyl amine *para*-amino-phenyl stibinate was made by the German I. H. Farben and marketed under the name neostibosan. It is now made by Winthrop and Co. and marketed under the same name.

countries, especially those in the Sudan, in China and in some of the Mediterranean areas, have not found that this short course is sufficient (*vide supra*). In any case, if the economic aspect does not predominate, it is probably safer to extend the course to twelve injections, but, when it is a matter of curing the largest number of persons with a given quantity of the drug, eight injections constitute probably the optimal course, according to Indian experience.

**Response to treatment**—Little notice should be taken of the immediate response of each patient to the treatment, especially when the daily dosage is adopted, as, at the conclusion of a course of treatment, which the subsequent history of the patient shows was successful, the patient may show very little improvement even the fever remaining until after the last

in an average case

After three weeks the spleen should be considerably reduced, the patient should be gaining weight—he may lose weight for the first two weeks—the leucocyte count should be above 6000 per cmm and he should be free from fever. When he is in this state the patient is probably cured, if not, he may be going to relapse, and a second course of injections may be necessary. In some cases how-

ever progress is very slow, and unless there is a definite return of fever, which is not due to some complicating infection, it is probably advisable not to embark too readily on a second course but to wait a few weeks before starting it. In the relapsing case the temperature usually mounts slowly, any sharp rise during the course of treatment is generally due to some coincident infection—malaria being by far the commonest in India. In most

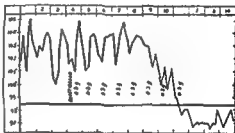


Figure 36 A characteristic response to treatment in an average case

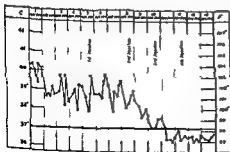


Figure 37 Early response to neostibosan treatment, the temperature remained normal subsequently

cases in which malaria supervenes, it is obvious that the disease must have been latent, and when patients come from a malaria endemic area it is advisable to give a course of quinine or other anti-malarial drug as a routine when the antimony course is completed.

Patients afebrile at the beginning of treatment not uncommonly show a febrile reaction, in the form of a daily rise of temperature or a sharp rise after each injection.

**Urea stibamine**—Urea stibamine has been extensively used in India and in a series of cases treated in our hospital gave very good results. It is slightly more toxic than neostibosan and cannot be given in such large doses, we found that 0.25 gramme was the largest dose that it was advisable to use, but most workers advocate 0.2 gramme as a maximum, the injections should be given on alternate days or three times a week, but not daily. The initial dose recommended is 0.05 gramme, the second 0.1 gramme, the third 0.15 gramme, and the fourth and fifth 0.2 gramme. The dose

must be used. It should be given intravenously. It should be given into the subcutaneous tissues or if given intramuscularly, it causes much more pain than neostibosan, but not the very severe reactions caused by sodium antimonyl tartrate. The course of treatment is from twelve to fifteen injections.

**Other antimony preparations**—Neostam gave satisfactory results in our cases. The dosage is much the same as for neostibosan. Antimosan and foudadin are aromatic trivalent compounds, a cure can be effected with either, but they are not so satisfactory as the pentavalent compounds for the visceral form of the disease, about twenty injections being required.

**Complications associated with antimony treatment**—Whereas with the trivalent salts of antimony, coughing, vomiting, joint pains, and the more serious lung complications commonly occur, with the pentavalent compounds, complications are rare. With neostibosan practically the only complication that ever occurs is a sharp rise of temperature on the day of the injection. This may be accompanied by vomiting. Very rarely this is due to some idiosyncrasy on the part of the patient, and the dosage has to be modified until tolerance is established, but more often it is due to some defect in the solution. We have never traced this to the drug but always to the distilled water in which it is dissolved, since the use of a fresh supply of distilled water has always eliminated the reactions.

With some of the pentavalent compounds, but very rarely with neostibosan, a condition suggesting anaphylactic shock occurs. Usually this does not follow the first injection but one of the later ones, the fifth or sixth, thus suggesting that the patient has been sensitized. This reaction has not been observed when daily injections are given, but has been reported in a few cases in which wider spacing of the injections was adopted. A few minutes after an injection, the patient's face becomes puffy, and an urticarial rash appears all over the body, the voice becomes husky, and the patient has difficulty in breathing, he becomes collapsed, and the pulse is imperceptible at the wrist, he often has diarrhoea and vomiting, and he may become cyanosed and unconscious for a few minutes. Recovery is usually rapid and is accelerated by an injection of solution of adrenaline hydrochloride and the administration of a diffusible stimulant. For the continuance of the treatment, the best course is to employ another compound and to begin with minute doses.

With higher doses of urea stibamine and of some of the other compounds, hæmorrhages from the gums, nose, and stomach sometimes occur. We have also seen retinal hæmorrhages and in one or two cases cerebral hæmorrhages have been suspected.

**The aromatic diamidines**—In our present state of knowledge, great caution should be exercised in using these drugs (*vide supra*) and they should be reserved for antimony resistant cases only. The dosage recommended below is that used by the writer who has treated well over a hundred cases with 4,4-diamidino diphenyl ethylene (stilbene) and thirty or so with 4,4-diamidino diphenyl pentane. The immediate reactions described below have been more prominent in the case of the former drug and the late sequel has only been noted with this drug but our experience with the latter has been too short and too recent for us to say that the neuropathological sequel described below does not occur.

They are supplied in the form of a white powder in sealed ampoules this is dissolved in distilled water to make a 1 per cent solution and given intravenously. The injections are given daily and very slowly. The maximum dose should not exceed 1 milligramme (0.001 gramme) per pound weight of patient. To adults irrespective of size and condition (because we have found that weak emaciated individuals stand the drug best) we give 0.020 g. as the initial dose. If this is followed by a very severe reaction we give 0.035 g. next day but precede the dose by an injection of 0.20 c.c. of 1 in 1000 adrenaline. If the reaction is mild we increase the dose to 0.050 g. but still give the adrenaline, or if there is no reaction we make the next dose 0.070 g. without adrenaline. The doses are increased as rapidly as possible by 0.010 g. or 0.020 g. according to the reactions up to the point of patient to the nearest milligramme whenever there is a marked reaction possible to omit it after the

maximum has been reached.

Children stand the drug better than adults we usually start with 0.010 g. and increase the dose by 0.005 g. to well over the 0.001 g. per pound maximum. In a few cases we gave the drug intramuscularly it was distinctly painful and caused a sharp local reaction but produced no abscess. The effect seemed to be about as good as when it was given intravenously but we were slightly bolder with our dosage as there was practically no general reaction.

We gave 10 injections in the majority of cases. This meant a varying total dose. It is probably safe in our present state of knowledge to aim at a total dose of not less than 0.750 g. per 100 pounds weight of patient and 1.000 gramme for resistant cases. Other workers have recommended a maximum of 0.001 g. per kilogramme but in the writer's experience some of the worst reactions followed the earlier injections which were always small and as he considers that it alternately to risk

and greater total doses in his series obtained cures with total doses varying from 0.750 g. to 4.900 g.

The good effects of treatment with the aromatic diamidines are not immediately apparent and in the vast majority of cases the temperature remains until after the course is complete in fact in many the first few injections appear to cause an exacerbation of all the symptoms. The temperature usually falls to normal a day or two after the last injection.

about a week later there is a sudden very rapid decrease in the size of the spleen, and the patient then begins to put on weight (see figures 38, 39 and 40)

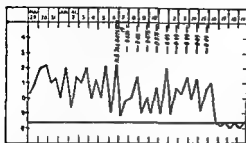


Figure 38 Response to diaminodilstibene, no fall of temperature until course is complete the usual response

loss of control of the bowels and urine and loss of conjunctival reflex, in the worst case in the writer's experience, the patient, a well-developed and healthy looking man with no discoverable abnormality except an oriental sore, who had received a dose of less than 0.0005 gramme per pound body weight, remained unconscious for about an hour, but recovered completely in another hour or so

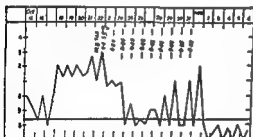


Figure 40 Response to diaminodilstibene very early fall usually results in a subsequent febrile reaction

*The reactions and sequelae* — Some reactions will be noticed in almost every case. The mild reactions include a headache, flushing of the face, sweating and a burning sensation all over the body. In the more severe cases the headache will be intense, there will be giddiness, faintness, palpitations and epigastric pain and vomiting. The most severe symptoms will be collapse, unconsciousness,

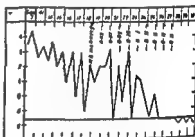


Figure 39 Response to diaminodilstibene, earlier fall of temperature

As noted above, most of these symptoms can be obviated, or reduced to a minimum by a small dose of adrenaline before the injection of the drug, and a moderate dose after the injection will usually relieve the patient rapidly. Where vomiting is prominent, this can be reduced to some extent by giving the drug on an empty stomach, but otherwise it is better to give it not more than two hours after a meal.

In about twenty cases, that is in over half the patients actually seen by us subsequently, a curious neuropathy occurred, namely, a subjective disturbance of sensation over various parts of the trigeminal nerve area, hyperæsthesia, paræsthesia, anæsthesia, and formication, and loss of sensation to light touch but preservation of the sense of pressure and pain. The first symptom is usually numbness of the area and is noticed about three months after the course is completed. The condition has persisted in one case for nearly two years, it showed little increase from the time we first saw the patient, five months after discharge from hospital, and has now decreased slightly (see figure 41).

Several patients have been treated with large doses of aneurin without effect, but subjective improvement has appeared to follow the (empirical)

administration of cobra venom, intramuscularly, in doses of 0.1 c cm rising to 1.0 c cm 1 in 100,000, every third day, in a number of cases



Figure III Affected areas in three cases of post-diamidino-stilbene neuropathy

### Subsidiary treatment

Very little subsidiary treatment is of any value until the course of specific has been completed indeed, whatever other treatment is given nothing should be allowed to interfere with the course of injections once they have been begun. When there are complicating infections such as malaria and hookworm disease the kala azar should be treated first. It has been suggested that heavy hookworm infections diminish the effect of the specific kala-azar treatment, there is no evidence that this is the case but treatment of the hookworm infection should always be delayed until one course of antimony has been given, though it is not necessary to wait to see if the cure of the kala-azar is complete.

The blood picture will soon return to normal, but this may be accelerated by a course of ferrous sulphate, 9 grains a day for two weeks. In cool climates or in the cold weather in India malt and cod liver oil and in the hot weather, compound syrup of hypophosphites, or some other suitable tonic, should be given during convalescence.

**Diet**—As a rule it is not necessary to enforce any severe dietary restrictions unless this is indicated by special symptoms. Some patients are always attacked by diarrhoea when allowed a full diet, and when the fever is at its height it is inadvisable to allow a high protein diet, but most patients have a good appetite and do well on a liberal diet. Our hospital patients are allowed an ordinary diet unless there is some special contra-indication but for out-patients and others not immediately under control a vegetarian diet with only a little rice plenty of milk and eggs is recommended.

T- - - - -

**Treatment of resistant cases**—Other complications should be treated symptomatically. A resistant case may be defined as one in which a cure is not effected by an ordinary course of treatment which will cure from 90 to 95 per cent of patients, it is therefore a relative term, but nevertheless

patients seem to be divided fairly sharply into two classes, the ordinary and the resistant. When a patient who has a clear history of having had full course of treatment a month or two before is found still to have visceral infection, he should be classed as a resistant case and treated accordingly.

Early experience with the drugs of choice in resistant or 15 injections in resistant a mean relative dose of 1 C cured (apparently) 22 out of 25 antimony-resistant cases.

Previously, the course of neostibosan that we gave in a resistant case (adult) was as follows —

Twelve injections in twelve days, beginning with 0.2 followed by 0.3, 0.4, and subsequently 0.5 gramme daily, an interval of twelve days, a second series of twelve injections, beginning with a dose of 0.3 gramme, another interval of twelve days, and a third series of twelve injections, beginning with 0.3 gramme.

If the patient shows little sign of improvement during the first series of injections, the second series is given. Of this, 1 part each not occur, a larger dose is injected a day or two later. The object is to produce a very severe local reaction. The turpentine injections are given coincidentally with the antimony injections.

In one of the most resistant cases the writer has ever encountered, a cure was effected by the application of the same principle in a slightly more primitive form by a practitioner of the 'indigenous' system of medicine who placed a vesicatory plaster on the patient's abdomen which caused the whole abdominal wall down to the muscle to slough and left a deep ulcer the size of the palm of the hand, when the ulcer healed the kala-azar was cured.

When one antimony compound has been used throughout without success, a change to another compound should be tried.

Treatment of post kala azar dermal leishmaniasis — Antimony seems to be the only specific for post-kala-azar dermal leishmaniasis, but a cure is not nearly so readily effected as in the visceral form of the disease. Preliminary experience with diamidino-stilbene does not suggest that it is of any value in this condition. We have generally used one of the pentavalent compounds, but in a few obstinate cases good results have followed the use of the newer trivalent compounds, antimosan and foudrin.

The ordinary course of injections, as recommended for the visceral infection, should be given, but the injections should be on alternate days or even more widely spaced. One course may be sufficient. The nodular lesions will usually show distinct improvement during the first course of injections, but the hypopigmented lesions usually remain unchanged, gradually regaining their pigment during the course of a month or so. Similarly, the shrinking in the nodular lesions will continue for some time after the end of the course of treatment, a period of at least two months should therefore be allowed before it is decided that another course will be necessary.

Injection of a 2-per-cent solution of berberine sulphate into the nodular lesions is usually followed by their shrinkage, but this is not a very

practical method when lesions are extensive. We have seen a few cases improve on large doses of potassium iodide, given up to the point of producing iodism especially cases in which the nodular lesions were very extensive, the nodules may undergo ulceration, but heal rapidly when the potassium iodide is discontinued.

## PROGNOSIS

stage without any symptoms except slight anæmia and great splenomegaly.

Death usually occurs from some complicating infection, such as dysentery or pneumonia, or from cancer of the oris. In infants and young children the disease runs a far more acute course, and the duration is often less than six months.

Rarely, in India at least but apparently much more frequently in other countries, especially in the Sudan the disease runs a much more rapid course, after two or three months of high fever purpuric spots appear, there are profuse hæmorrhages from the mucous membranes, and death follows rapidly.

From experience in India, the prognosis can be summarized as follows: if no treatment at all is given, 75 per cent of patients will die, the majority within a period of two years. In the infantile form the natural duration of the disease is shorter probably about a year. If a full course of treatment with arsenic is given, the prognosis is much better.

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there were two deaths and five relapses, that is to say an apparent cure rate of 93 per cent.

If the disease has lasted more than a year, the patient may be very weak and emaciated and have developed various complications, e.g. cirrhotic changes in the liver. Although uncomplicated cases of long

more readily

In Bengal, in about 5 per cent of treated cases post-kala azar dermal leishmaniasis develops. This sequel is apparently much rarer, or even unknown, in other localities.

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# ORIENTAL SORE

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Definition — Cutaneous leishmaniasis

Geographical distribution — Occurs throughout the world than any of the other diseases.

In Europe several cases have been reported from the southern portion of the continent. Cases from Calabria and from several other parts of the south of Italy.



Figure 42 : Distribution of espidemia and leishmaniasis in the American continent and the West Indies.

in the West Indies and well away from the endemic areas. Both diseases occur. Cases have been reported from the French Sahara, the French Sahara, and from several other parts of the continent.

In India, the disease is found over the whole of the western and drier portion of the Indo-Gangetic plain; the endemic area extends north into the North-West Frontier Province and Baluchistan and down the west coast of the peninsula as far as Cambay in the Bombay Presidency and east as far as Delhi, further east as far as Benares sporadic cases are reported

In Oceania, instances of oriental sore have been reported from North Queensland

**Distribution of oriental sore compared with that of kala-azar**—Kala-azar and oriental sore are very rarely present in the same locality, both diseases occur in Crete, and in some parts of Asia Minor they occur side by side and in fact are reported to have appeared simultaneously in the same family. In India, oriental sore is found in the dry western half of the Indo-Gangetic plain, whereas kala-azar is confined to the moist

benign oriental sore might prove a protection against the then deadly kala-azar. It has now been satisfactorily shown that cross immunization does not occur

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*P. papatasi* and *P. sergenti*, which probably transmit oriental sore, are common sand-flies of the dry areas

**Climatic factors**—It would be difficult to correlate the various climatic conditions in the endemic areas, and, as they are so widespread, it seems improbable that there are many climatic factors common to these areas. Most of the areas of greatest activity, however, lie between latitudes 20° and 45°N. These areas have a very hot season, some of them as hot as in any part of the world, and a short cold season in which the night is dry. Most of them are dry and on desert land, and the disease appears in the eastern portion of the western

**Epidemic features**—In the areas where it occurs the disease is usually endemic, but the incidence varies considerably from year to year, and very frequently assumes epidemic proportions

te, the number of sand-flies decreased

where the debris provided ideal cover was an epidemic of oriental sore

amongst the troops who helped to clear the area

In Iraq there is a popular association, both with reference to season and locale, between dates and oriental sore, the explanation might well be that sandflies feed on ripe dates (see p. 145 and Plate V)

Dostrowsky in Palestine reported that family incidence was considerable but this has not been the experience of many other observers and in areas where the disease is sporadic it is by no means uncommon in a family of children for one child alone to be infected

Seasonal incidence — Practically all observers have noted that there is a definite season of onset but this season is not identical in the various endemic areas Dostrowsky reported that in Palestine in most cases the lesions first appeared between the months of September and April i.e. immediately before and during the rainy season Carton and Bacque said that most of the cases in northern Africa were infected in July August and September Yakimoff and Schockov reported that out of 48 cases seen in Turkestan in January, in one case the sores appeared in June in 7 in July and in 40 in August In Iraq the first cases are usually seen in July the monthly incidence rises up to September or October, after which it begins to fall In the North West Frontier Province and in the Punjab the first cases appear in June and July August and September are the months of the highest incidence A report on oriental sores acquired in Quetta (Goodall) suggested that there the months of maximal infection were September and October The month of infection or if about three months is allowed as an incubation period the first appearance of the lesions usually corresponds with the maximum sand fly incidence

Age race and sex incidence — Persons of all ages and races and of both sexes appear to be equally susceptible In the heavily infected areas children form the bulk of the patients but this is only because the adults have acquired a degree of immunity from having been infected and cured during childhood For the same reason foreigners in endemic areas appear to be particularly susceptible

## ÆTIOLOGY

The causal organism — *Leishmania tropica* (Wright 1903) is a protozoon of the family Trypanosomidae it is indistinguishable morphologically and culturally from *L. donovani* the causal organism of kala azar  
two parasites  
in the round  
cells in the  
ulcer where it  
*Phlebotomus*  
passes into its  
invasion of th  
has not been  
rare accident  
lymphatic cl  
along the course of the vessel (see plate V figure 5)

In some small animals a generalized blood infection occurs

**Transmission**—Attention was first focused on the sand-fly as a possible transmitter by Wenyon (1911), who found 6 per cent of the sand-flies in Aleppo, an endemic area, infected with a leptomnad. Work on sand flies was continued by the Sergents and others during the next few years, but no very important observation was made. In 1919 Acton, by making comparative anatomical 'spot' diagrams of oriental sores and of sand-fly bites and showing the marked similarity between these diagrams, added further support to the sand-fly hypothesis (see figures 43 and 44)

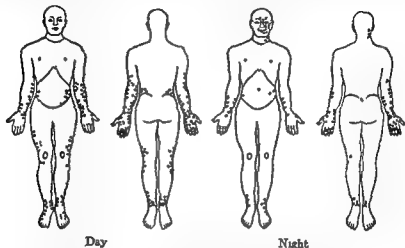


Figure 43 Spot diagram of the position of sand fly bites during the day and night

Sergeant, Sergeant, Parrot, Donatien and Beguet (1921) produced oriental sore in volunteers in a non endemic area by inoculating crushed sand-

and *P. sergeni*, natural carriers of *L. tropica*, and that in special circumstances they were capable of transmitting the infection from host to host. In Italy, *P. macedonicum* has been incriminated as the transmitter.

More recently, Adler and Ber (1941) have actually produced 18 oriental sores in 5 volunteers by the bites of artificially infected sand flies.

The mechanism of transmission is believed to be similar to that of kala-azar. The sand fly becomes infected by feeding on the indurated

ment of the host's skin so that, if the fly lives long enough it can convey the infection when

a sore can produce the lesion, mes occurs, but it is equally certain that it is not the human source of transmission.

**Animal reservoirs.**—The sporadic incidence of oriental sore has suggested that there is some non human reservoir of infection, and lizards

infected in nature. In certain animals, as well as producing local lesions, *Leishmania tropica* causes a generalized infection, so that it is possible that sand-flies may become infected by simply feeding on the blood of infected animals. In Turkmenistan, the gerbil, *Rhombomys opimus*, has been found infected in nature, to the extent of 60 per cent of specimens examined. Thirty-five per cent of sand-flies living in their burrows have been found infected. These animals therefore obviously play an important part in the ætiology of the disease in desert areas.

**Immunity**—Some immunity against subsequent attack is conferred on the patient. This is demonstrated in the epidemiology of the disease by the fact that in endemic areas the indigenous adult is comparatively immune, most of the sufferers being children and immigrants. Advantage has been taken of this fact, and in certain countries women have inoculated themselves with oriental sore on some covered part of the body as a prophylactic against the disfiguring effect of a sore on the face. That this immunity is not complete is shown by the facts that auto-inoculation is not uncommon and that second attacks sometimes occur after the original ulcers have healed completely, of forty-eight cases seen by Yakimoff and Schockov in Turkestan eight had been attacked previously, Marzinowsky and Schourenkoff stated that experimentally produced sores in man only conferred immunity when they ran their natural course, abortive lesions and those subjected to treatment at an early stage failing to produce immunity. It is also claimed that there are different strains of *L. tropica*, and that immunity is not complete against heterologous strains.

There is no reason to suppose that oriental sore confers immunity

## PATHOLOGY

The infection is a localized one and there is no general reaction to infection. A very definite tissue reaction is caused by the local presence of the parasite, the macrophage apparently playing the main part in this reaction. Considerable infiltration of all the layers of the dermis by these cells, many of which contain parasites, extends into the subcutaneous tissues. Giant cells are sometimes present. The parasites apparently have a special affinity for the endothelial cells of the arterioles and capillaries, which become parasitized and swollen; the channels become blocked, and necrosis may follow. The cellular proliferation continues and spreads centrifugally, interfering further with the blood supply of the epidermis and reducing it by pressure to a thin membrane which is easily damaged by trauma.

Pyogenic organisms eventually find their way through this damaged epidermis, and ulceration occurs. The pyogenic organisms invade the



down growths from the epithelium Leishmaniae do not invade the epidermis

Eventually the granuloma is invaded and superseded by fibrous tissue and, when the superficial septic process resolves, the epithelium grows in from the edges of the ulcer, a scar, consisting of a thin covering of epithelium over hard fibrous tissue, is left

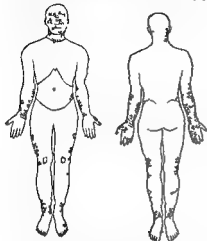


Figure 44 Spot diagram of the sites of sores in Indian troops in Iraq

exposed parts of the trunk. The scalp, the palms of the hands, and soles of the feet are not affected. A 'spot' diagram (after Acton) shows the distribution of the sores in Indian troops in Iraq, these soldiers wore 'shorts' and puttees, i.e. their knees were bare (see figure 44)

**Number of sores**—The sores are sometimes single, but more often multiple. Occasionally very many sores appear on different parts of the body, figure 4 (plate V) shows a patient with 239 sores

**Absence of general symptoms**—As a rule general symptoms do not accompany the appearance of the local lesions, but in some cases there is a history of slight fever lasting a few days

**The typical sore**—A small itching red papule surrounded by a narrow pink halo is first observed at the site of inoculation, this increases in size and becomes a patch of dry scales that vary in colour

increases in size and  
into a large raised  
usually breaks down

under the scab and an ulcer forms the ulcer which is small at first spreads but is usually more or less circular, has clean cut edges a

## PLATE V

Fig 1—Fungating sore on cheek

Fig 2—Oriental sores on the back of the hands of a British soldier these are beginning to heal

Fig 3—One month later now completely healed repigmentation commencing in left hand

Fig 4—Patient with 239 sores

Fig 5—Ulcerating sore on finger with lymphatic spread nodules appearing along the course of the lymphatics

[Figures 2 and 3 after Goodall (1937) others after Shah (1941)]

PLATE V (Oriental sore)



Fig 1

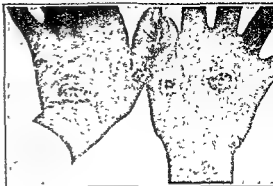


Fig 2

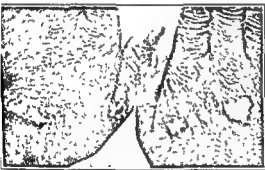


Fig 3



Fig 4



Fig 5



utaneous leishmaniasis in a chicle-gum worker in Yucatan. The lesion on ear, one

sloughing and later a granulating base and is surrounded by an area of red induration about a quarter of an inch in breadth. The ulcer exudes a sero purulent discharge which may dry and fill the ulcer with a hard dry scab which is difficult to remove. If it is left untreated, after a year or so, the sore may heal, leaving a depressed pink or white scar which may cause considerable disfigurement, more especially when contraction of the scar tissue occurs. The ulcerating form is always secondarily infected with pyogenic organisms, and in cases of long standing a streptothrix infection which eventually replaces the leishmania is not uncommon.

**Other clinical types**—Other forms of open lesion are the eczematous and the verrucose. In the latter form a cauliflower-like growth may involve a large area of the instep for example.

There are many non ulcerating forms, the commonest of which is the fleshy nodule that does not break down. There are also the keloid and the lupoid forms.

The lymph channel draining caused by occasionally found in the lymphatic glands. In some cases subcutaneous nodules appear along the line of the lymph channel these eventually break down and become separate ulcers (see figure 5 plate V).

The complications are those commonly associated with open ulcers. Lymphangitis has already been mentioned less often phlebitis and erysipelas occur. When the scars contract they leave disfiguring deformities e.g. ectropion.

### DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

After considerable experience with this condition it is easy to make a diagnosis on clinical grounds alone with some degree of certainty, but the laboratory method is quite necessary when a secondary infection has led to the destruction of the parasites except in the deeper portions of the ulcer. After about a year it is seldom possible to demonstrate leishmaniae, and it is probable that they have died out and that the ulceration is maintained by the secondary organisms.

No parasites will be found in the pus taken from the centre of an ulcer, the secondary infecting organism alone being present. There are several ways in which the parasites can be demonstrated, if the lesion has not ulcerated or if the first attempt fails. The method which is most reliable is to make a smear from the serous fluid which will subsequently come out. Or if this serous fluid is drawn up into a sterile pipette it can be placed into Nicolle Novy and MacNeal (NNN) or Senekjvics medium to obtain a culture of the organism.

The smear should be examined after staining by Leishman's or by Giemsa's method. When any surgical treatment is undertaken a piece of the margin of the ulcer can be removed and a smear made from the cut edge of this piece, or a smear can be made from the deep scrapings of the ulcer after it has been cleaned and washed with saline.

Jessner and Amster obtained specific skin reactions in dogs and human beings by injection of a dilute blood-free vaccine of flagellates. By separating the polysaccharide and protein fractions of the antigen Senekjic believes that he can distinguish between current and past infections.

**Differential diagnosis**—The condition must be differentiated from all other forms of skin nodule, boil and ulcer. It is unnecessary to deal fully with all the non-specific boils and ulcers following an injury, or with syphilitic and varicose ulcers of the legs, but a few specific conditions, chiefly tropical or subtropical in their distribution, deserve special mention.

Each of these conditions has its characteristic appearance, which is distinct from that of the typical oriental sore, but all of them as well as oriental sore may vary from the typical. A knowledge of the geographical distribution of these diseases and of the recent movements of the patient is a most essential preliminary to accurate diagnosis, the final test is the demonstration of the specific organism, which in oriental sores of moderately short duration presents little difficulty.

**Ulcus tropicum**, the sloughing phagedenic ulcer of the tropics, is mainly confined to the legs and occurs in ill-nourished coolies. It usually begins with a water-blister or bleb, and sloughing is an earlier and more prominent feature. Scrapings from the base of this ulcer, after the slough has been cleaned away, will show the characteristic flora, a spirochæte and a fusiform bacillus.

**Yaws** is a disease of aboriginal races and occurs in all parts of the body, and the lesions are rarely single, the typical lesion is raised above the skin level, and, when the scab is removed, the characteristic 'raspberry' appearance is seen. *Treponema pertenue* is found in the lesions, and the Wassermann reaction is positive.

**Tuberculosis of the skin** is not uncommon in the tropics, and, whether in the form of a tubercle, which is more usual, or of an open ulcer, it may be mistaken for oriental sore, the extreme chronicity of these lesions and the characteristic appearance in the histological sections will settle the diagnosis.

The localized, raised and indurated lesions of leprosy may be mistaken for the non-ulcerating form of oriental sore, microscopical examination will settle the diagnosis. Leprotic ulcers will present less difficulty on account of their painlessness. In either case other manifestations of leprosy should be looked for but the presence of these does not necessarily exclude oriental sore.

**Veld sore** begins with a vesicle and is usually shallower than the oriental sore, it generally has an undermined edge and is very painful. *Corynebacterium diphtheriæ* is easily isolated in the early stages, but chronic sores of the two conditions present considerable difficulty.

A primary syphilitic sore on the lip is not at all unlike an oriental sore, nor is a tertiary gummatous ulcer. Microscopical examination will settle the diagnosis rapidly in the first case, and in the second a positive Wassermann reaction will be suggestive but not conclusive.

## PREVENTION

**General**—The general measures will include the avoidance of the source of infection and of the transmitting sand-fly.

All close association with infected human beings and infected dogs should be avoided. A dog-destruction campaign should be undertaken where these are suspected as carriers.

Sand-flies are very local in their habits, and it is often possible to get out of their range by moving a tent or hut only a few hundred yards the banks of rivers and old brick or mud walls are their favourite habitats, but unfortunately sand-flies will also live in cracks in the ground. In special circumstances sand-fly control may be worth attempting (see p 320)

**Personal**—These will include the use of a sand-fly net (45/46 mesh), insect repellents (see p 119), and possibly prophylactic inoculation

The production of immunity by the injection of dead vaccine has not yet reached a satisfactory stage. Lawrow and Dubowski (1937) obtained very satisfactory results by the induction of single sores on the covered parts of the body by the injection of 0.1 to 0.2 ccm of living cultures. The sores appear in two to six months, increase in size for a time, and eventually heal in about twelve months' time.

### TREATMENT

The cure of oriental sore is not so satisfactory as that of the visceral infection, kala azar. This is evident from the large number of different forms of treatment that are advocated. No satisfactory comparative study has been undertaken since the newer forms of treatment were introduced, and most of the opinions expressed by different workers are based on clinical impressions.

The treatment may be (i) local or (ii) general. The local forms of treatment advocated can be considered under the headings (a) surgical treatment, (b) application of specific drugs, (c) physical measures, and (d) local injection of specific drugs. The general measures consist in the intravenous or intramuscular injection of various antimony preparations.

(i) **Local**—(a) **Surgical** In the pre-antimony days, surgical measures were mainly relied upon, e.g. vigorous scraping with a Volkmann spoon

adhesive strapping and leaving it without further dressing for a week or more, after thorough scraping and treating with liquefied phenol under an anaesthetic, has given very satisfactory results and is probably the treatment of choice for the more advanced septic ulcers. For small ulcers direct application of liquefied phenol without previous scraping is said to be very satisfactory. Castor-oil dressings have given satisfactory results in some workers' experiences.

(b) **Application of specific drugs**—Those recommended include potassium antimonyl tartrate ointment 2 or even 4 per cent powdered potassium permanganate mercuric chloride mercurous chloride, methylene blue ointment, and powdered sulphonamide, good results have been claimed with each of these drugs by certain workers, but none has proved generally satisfactory.

towns this is usually obtainable ready for application in the form of 'dry ice', otherwise a suitable stick can be prepared from a carbon dioxide-gas cylinder. The dry ice is applied directly to the sore and held there for at least two minutes by the clock. There is a severe reaction with blistering, but when this has subsided the ulcer usually heals.

(d) **Local injections**—Emetine hydrochloride has been used very often, 20 minims of a 5 per cent solution are injected into the margins of the sore. Mepacrine (atebrin) hydrochloride was suggested some years ago for local infiltration and according to some reports, a few of which are recent, is very satisfactory.

The local injection of berberine sulphate has in our hands produced some excellent results and is, in the writer's opinion, the best of the drugs used for local infiltration, the drug appears to have a direct specific action on the parasites.

If the ulcer is septic, hot magnesium sulphate fomentations and frequent dressings should be used for a few days to make the wound as clean as possible. A 2 per cent solution of berberine sulphate is used, this is injected by means of a tuberculin syringe into the indurated area surrounding the ulcer, about six injections will be required for each ulcer in order to infiltrate the whole circumference of the ulcer, but 1 ccm of solution will usually be sufficient for an average sized ulcer. There will usually be some inflammatory reaction, which should be allowed to subside before further injections are given, it will usually be possible to give the injections once a week. From three to six treatments will effect a cure. If there are multiple sores, not more than two or at the most three should be treated at one 'sitting', but treatments can be given daily, the ulcers being taken in turn. This treatment however cannot be recommended when there are more than half a dozen ulcers.

(ii) **General**—The intravenous injection of tartar emetic solution was applied in the treatment of oriental sore immediately after it was introduced for the treatment of kala azar. Good results are undoubtedly

the writer treated a number of cases with stibosan and later, neostibosan. Cures were effected but on the whole the progress was disappointingly slow. More recently we have used the aromatic trivalent antimony compounds e.g. foudadin, with rather better results.

The dosage for neostibosan has already been given under the treatment of kala azar (see p 168). It is probably better to give the injections on alternate days rather than daily, and ten to twelve injections will usually be necessary.

Foudadin is supplied in ampoules as a 63 per cent solution the starting dose is 15 ccm and the maximal single dose 5 ccm. The injections are given intramuscularly on alternate days or three times a week, and eight to ten injections are usually sufficient.

It is too early to be dogmatic but the evidence up to the present suggests that the aromatic diamidines, some of which are so successful in kala azar, are quite useless in this condition.

To summarize, in those cases in which there are single or only a few

surgical treatment. Until the sore is obviously healing simple antiseptic powder should be included in all dry dressings. A judicious combination of surgical treatment with antimony injections will produce the best results in cases with very numerous extensive ulcers.

### PROGNOSIS

Under normal circumstances there should be no question of mortality from oriental sores, though no doubt many lives have been lost as an indirect result of these sores, especially when septic complications have followed. The two important points are the time taken in healing and the scarring left behind.

The course of an untreated sore is about a year, when eventually it heals it always leaves a disfiguring scar.

Under efficient treatment simple sores will often heal in two to three weeks, but the average time taken for septic sores is probably at least two months.

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Lesions occur almost always on uncovered parts of the body, on the ears, face, neck, arms, wrists, legs and ankles, they are usually multiple

The ulcerating type commences as a small red itching papule or as a localized papular erythema. The papules go on to pustule formation, break down and form small ulcers. The ulcer is surrounded by an edematous area which eventually forms an ulcer of 9 or 10 centimeters usually round, but may be irregular, but later become a narrow area of induration. There is a purulent exudate. In many instances there is lymphatic involvement following on local infiltration around the ulcers, there may be subcutaneous nodule formation along the course of the lymphatics, and the glands become enlarged and painful, this glandular enlargement is not entirely due to septic invasion of the ulcer, since leishmaniae can be recovered from the glands. The glands often fail to regain their natural size after the local condition is cured.

The papillomatous type commences in much the same way, but the red papule, instead of becoming a pustule, increases in size and exudes a serous fluid which may form a crust, under this crust, which soon scales off, lies the thin but intact epithelium. The non-ulcerating type may eventually, after many months or even years break down and become an ulcer.

The mucosal lesions.—As already stated, the frequency of the occurrence of the mucosal lesions varies in the different areas of activity of the disease. Mucosal lesions are rare, but in the nose, mouth and pharynx, Klotz and Lindenberg (1923) report that 25 per cent of those patients who have had cutaneous lesions for more than two years suffer from mucosal lesions, and Villela, Pestana and Pessoa (1939) that in practically all untreated cases of cutaneous lesion, there is infection of the nasal mucosa which may or may not break down. In 12 cases without clinical symptoms referable to the nasal mucosa, 5 showed small lesions, and in the rest, smears made from the mucosa showed leishmaniae.

When they occur, the mucosal lesions usually appear 11 to 18 months after the cutaneous lesions have begun. The nasal lesions commence as an indurated area followed by the formation of a mass which spreads with time. It is estimated that 78 per cent of the lesions are in the nose. An ulcer may form in the nose, mouth and pharynx may be involved and destroyed. The bones and the tongue are not, however, attacked. The patient when untreated, usually dies from septic absorption, pneumonia, or starvation from blockage of the passages. Costa (1916) described certain ocular complications which have occurred in this condition: a new growth in the centre of the cornea, and lesions in the lower eyelid accompanied by opacity of the vitreous.

#### DIAGNOSIS

This does not usually present much difficulty when there are early cutaneous lesions, the indurated edge of the ulcer is pricked and a smear made from the exudate will usually show leishmaniae (see ORIENTAL SORE). In older sores it may be difficult to find them.

In cases with mucosal lesions it is usually possible to find the leishmaniae by scratching the intact part of the mucous membrane of the nose.

and making a smear from the exudate. Smears from the lesions themselves will seldom show leishmaniae.

The intradermal test of Montenegro is a valuable specific test. This is done by injecting intradermally 0.1 c.c. of a suspension of a culture of *Leishmania brasiliensis* in 0.4 per cent phenol. Within 48 hours there is a sharp local reaction which persists up to 72 hours. The test first becomes positive after about a month and continues to be positive as long as the lesions remain. Complement fixation and agglutination tests have also been used.

The condition has to be differentiated from leprosy, frambæsia, blastomycosis and syphilis, it differs from the last named in that, in the leishmania infection bones are not attacked and, in syphilis the ulceration does not usually spread beyond the mucocutaneous margin.

### PREVENTION

The only absolute means of control is by anti sand fly measures, but little is known about the bionomics of sand-flies.

The thorough treatment of all cutaneous lesions must be looked upon as the only means of preventing the more serious mucosal lesions that can be applied at present with much hope of success.

### TREATMENT

This should be both general and local. The local treatment recommended for oriental sore (q.v.) can be applied for the cutaneous lesions in this infection but general treatment must also be applied to prevent the later development of mucosal lesions.

Vianna and Machado (1913) used potassium antimonyl tartrate by the intravenous route in this disease and thereby initiated a new era in the treatment of leishmaniasis. Antimony has been the mainstay in the treatment ever since.

The new antimony compounds have been used more recently, and foudair, most of 15, on alte.

Arphenamine preparations are sometimes used for the cutaneous lesions, but, whilst curing these (after 3 or 4 injections), they leave the mucous membrane infections intact, nasal ulceration usually follows eventually, and in the end antimony has to be resorted to.

Recently it has been claimed that atabrin injected locally and given by mouth at the same time is a specific for the cutaneous lesions, and yatrien given intravenously combined with foudair is said to accelerate the cure of the mucosal lesions.

For local application to the mucosal lesions, a bicarbonate of soda gargle for the throat and nose, followed by a wash of 0.1 per cent solution of tartar emetic is said to be useful. Another method is spraying with a 2 per cent solution of tartar emetic after anaesthetizing with a spray of 1 per cent cocaine plus 1 per cent phenol.

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**Definition**—Sleeping sickness is a specific disease confined to tropical Africa, characterized in its early stages by fever, glandular enlargement, and anæmia, and, in its later stages, by progressive involvement of the central nervous system, it is caused by *Trypanosoma gambiense*, or *Trypanosoma rhodesiense*, protozoa of the family Trypanosomidae, which are transmitted to man by tsetse flies, flies of the genus *Glossina*

**Historical**—Since the beginning of the 16th century there have been sporadic references to a mysterious lethargy that fell upon the natives of certain parts of equatorial Africa, but with the further development of the slave trade and its penetration into new areas, the commercial implications became apparent, and the casual interest in this disease gave way to a more purposeful one. Slaves taken to the West Indies developed the disease shortly after arrival, and, though the disease did not spread there the slave became useless as a slave, and even if he did not die immediately he was a dead loss to the trader. The condition was attributed to home-sickness, but nevertheless it was observed that slaves from certain areas were more prone to 'brooding' than those from other slave areas. Trade in Africa itself led to the spread of the disease where it spread to the humanitarian and embarrassing intruders. During the first half of the 19th century, there was a steadily increasing number of references to *la maladie de sommeil* in medical literature, but no material progress in its elucidation was made.

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found trypanosome  
that it was the causal organism

(in 1890, Evans had demonstrated  
the tsetse fly as the causal organism in Africa) He demonstrated  
wild game were  
any disease from

the presence of the parasites in their blood

The first recorded finding of a trypanosome in the human blood was that of Nepveu, who, while looking for malaria parasites, found trypanosomes in the blood of a man in Algiers in 1890, but he did not recognize the significance of the observation. Forde (1901) was the first to observe

a trypanosome in a case that a trypanosome can be transmitted from cell to cell sleeping sickness.  
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The first Sleeping Sickness Commission (Royal Society) went out to Uganda in 1902 and Castellani one of its members, discovered trypanosomes in the cerebro spinal fluid of patients suffering from sleeping sickness but was more attracted by some streptococci that he also found. The second Royal Society Sleeping Sickness Commission operated from 1903 to 1906 with P. A. S. as its head. Not until 1906 did P. A. S. and his colleagues find the trypanosome in the cerebro spinal fluid of patients with sleeping sickness. The commission which proved that sleeping sickness was due to *Trypanosoma gambiense* and that it was transmitted from man to man by the tsetse fly *Glossina palpalis*.

Until its etiology had been thus established sleeping sickness was not recognized as a single syndrome though the natives of Africa themselves and the early clinical observers had noticed that those who had cervical glandular enlargements were liable to the *la maladie de sommeil* at a later date.

In 1910, Stephens and Fantham found trypanosomes in the blood of a man who had come from Rhodesia they considered that it differed from *T. gambiense* and named it *Trypanosoma rhodesense*. In the following

was quite distinct and that though similar, they were clinically distinguishable and later it was shown that they responded to treatment very differently.

Subsequent investigations have shown that certain other species of *Glossina* are capable of transmitting the infection but only two of these are of any importance namely *G. tachinoides*, as a transmitter of *T. gambiense* and *G. swynnertoni* as a transmitter of *T. rhodesense*.

In his work on nagana Bruce visualized only the direct transmission of the infection from animal to animal by the contamination of the

For the last thirty years much of the work has been of an epidemiological

have a common origin and the issue has now tended to become—under what conditions does the trypanosome found in cattle acquire the ability to infect man and conversely—when passed through bovines under what conditions will the trypanosome causing the Rhodesian type of sleeping sickness lose its properties as a human pathogen? The recent investigations

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investigated nagana, in 1895 he investigated the blood of cattle dying of this disease and proved that the parasites had demonstrated the same characteristics. He demonstrated that the parasites were found in the blood of wild game were the reservoirs of infection but did not themselves suffer any disease from the presence of the parasites in their blood.

The first recorded finding of a trypanosome in the human blood was that of Nepveu, who, while looking for malaria parasites, found trypanosomes in the blood of a man in Algiers in 1890, but he did not recognize the significance of the observation. Forde (1901) was the first to observe

a trypanosome in a case that in retrospect can be recognized clinically as sleeping sickness, but he did not know what the 'worm-like' body was. This same patient returned from Gambia to England, and Dutton again found the parasite in his blood, recognized it as a trypanosome, and named it *Trypanosoma gambiense*.

The first Sleeping Sickness Commission (Royal Society) went out to Uganda in 1902, and Castellani, one of its members, discovered trypanosomes in the cerebrospinal fluid of patients suffering from sleeping sickness, but was more attracted by some streptococci that he also found. The second Royal Society Sleeping Sickness Commission operated from 1903 to 1906 with Bruce at its head. Not unnaturally Bruce, remembering his work in the blood of the whole story, hurried through so much of his work of this to *Trypanosoma* as by the tsetse

fly, *Glossina palpalis*.

Until its aetiology had been thus established, sleeping sickness was not recognized as a single syndrome, though the natives of Africa themselves and the early clinical observers had noticed that those who had cervical glandular enlargements were liable to the *la maladie de sommeil* at a later date.

In 1910, Stephens and Fantham found trypanosomes in the blood of a man who had come from Rhodesia, they considered that it differed from *T. gambiense* and named it *Trypanosoma rhodesiense*. In the following year, Kinghorn and Yorke showed that this trypanosome was transmitted by another tsetse, *Glossina morsitans*. It was soon recognized that the geographical distribution of the disease caused by these two trypanosomes was quite distinct and that, though similar, they were clinically distinguishable, and later it was shown that they responded to treatment very differently.

Subsequent investigations have shown that certain other species of *Glossina* are capable of transmitting the infection, but only two of these are of any importance, namely *G. tachinoides*, as a transmitter of *T. gambiense* and *G. swynnertoni* as a transmitter of *T. rhodesiense*.

In his work on nagana, Bruce visualized only the direct transmission of the infection from animal to animal by the contamination of the proboscis of the tsetse, and later, in his work on human trypanosomiasis, he definitely stated that the fly was capable of transmitting the infection only for 48 hours, but later it was shown by numerous workers, led by Kleine (1909), that there was also cyclical transmission that is the trypanosome underwent a cycle of development in the fly before it was transmitted. Bruce (1910) at first placed the time interval as five weeks.

For the last thirty years much of the work has been of an epidemiological, centred round the fly and of which the problem at least they have a common origin, and the issue has now tended to become—under what conditions does the trypanosome found in cattle acquire the ability to infect man, and, conversely—when passaged through bovines, under what conditions will the trypanosome causing the Rhodesian type of sleeping sickness lose its properties as a human pathogen? The recent investigations



of Corson and others between 1930 and 1938 suggest that in both cases the trypanosomes show a considerable degree of stability (Corson, 1938).

### ÆTIOLOGY

**The causal organism**—As indicated above there are two species of trypanosome, *Trypanosoma gambiense* and *Trypanosoma rhodesiense*, though cause the two forms of sleeping sickness, they are protozoa of the class *Mastigophora*, family *Trypanosomidae*.

**Morphology and staining**—These two trypanosomes are morphologically indistinguishable in the peripheral blood of man. In the fresh specimen of peripheral blood the trypanosome is a spindle-shaped body with an undulating membrane running along its length. It can be seen easily as it disturbs the surrounding fluid. Further details of its structure the unstained specimen is unsatisfactory.

In the blood smear stained by Leishman's or Giemsa's method the trypanosome is usually 14 to 32  $\mu$  in length and 1 to 2  $\mu$  in width. It has a flagellum at the anterior end and a blepharoplast at the posterior end. The flagellum passes forward along the whole length of the body, and the undulating membrane, an extension of the flagellum, extends for about one-quarter of its length beyond the anterior end of the body. About the middle of the body is an oval shaped nucleus with a centrally-placed karyosome (seen only in the fresh specimen) which occupies about two thirds of the cytoplasm. It stains a light blue. It contains many small vacuoles. The trophonucleus, a small parbasal body and blepharoplast usually appear as one dark-red mass. The undulating membrane is a transparent pale-violet membrane.

There are two distinct forms of trypanosomes: the thin slender form that are the usual ones seen in the peripheral blood and the broad stumpy ones less frequently encountered. In the latter, the flagellum ends with the undulating membrane at the anterior end of the body of the parasite and there is no free flagellum. In both types of infection these two forms maintain about the same proportions: the slender form always predominating. In many intermediate forms are recognizable.

The parasite multiplies by binary longitudinal division of the trypanosome. In some forms, all stages of division may be seen in the peripheral blood.

In the cerebrospinal fluid the same forms will be seen, but they are more pleomorphic, and involution forms are frequently seen.

Crithidial forms, in which the blepharoplast is anterior to the nucleus, occur at certain stages in the insect vector (*vide infra*), but are not found in man.

Though the two species of trypanosome are identical in the blood of man when the infection is transferred to a laboratory animal, they exhibit certain differences, and in the case of *rhodesiense* infection a percentage of about 5 per cent, of the trypanosomes are 'posterior nuclear' forms, that is the nucleus is near or actually at the posterior end, and the blepharoplast is necessarily anterior to it.

**Culture**—Trypanosomes will survive for many weeks in NNN culture medium (see p 161), but there is little multiplication, and subcultures cannot be obtained.

**Distribution in the body**—Trypanosomes are found in the blood, lymph glands and lymph vessels in the early stages of the disease, and in

the later in the cerebrospinal fluid also. The parasites never invade the cells but are found in the connective tissue spaces of many organs in the intra cellular spaces of the brain and in the reticular tissue of the spleen and lymph glands.

**Pathogenesis in animals**—Both trypanosomes will infect laboratory animals rats guinea pigs and rabbits but *rhodesiense* produces a much more virulent infection in these animals further this latter parasite gives rise to the posterior nuclear forms referred to above which are only very rarely found when a *gambiense* infection is transmitted to a laboratory animal.

The infection can be transmitted to many species of wild antelope but only one species has been found infected with what appeared to be *T. gambiense*.  
 causes nagana (vide supra et infra)

In the tsetse fly, trypanosomes will be found in the gut mouth parts and salivary glands in all of which sites they multiply (see p 202)

**Strains**—As in many other infections there is evidence that in addition to the differences in species there are a number of different strains of the causal organism which vary in their virulence to man and animals and in their susceptibility to drugs. It seems possible that many if not all the puzzling variations in the pathogenicity of trypanosomes in different animal species and in drug resistance might be explainable on a theory of strain selectivity of vectors hosts and drugs.

**Immunity**—There is evidence of both natural and acquired immunity to trypanosome infection.

Normally man is resistant to infection with *T. brucei* less so to infection with *T. rhodesiense* but susceptible to infection with *T. gambiense*. Yorke and his co workers consider that there is evidence to suggest that in the presence of special conditions e.g. some other infection or dietary deficiencies the trypanocidal action of the blood of man is destroyed and that he then becomes susceptible to infection with *T. brucei* which once established acquires a degree of resistance to the trypanocidal action of human blood is capable of establishing itself in a normal individual and becomes what we know as *T. rhodesiense* finally as this trypanosome is transmitted rapidly from man to man by the tsetse fly its potentialities for infecting man become still more fixed it loses its pathogenicity for cattle though it still infects them and becomes *T. gambiense*. There are still many gaps in this attractive theory.

On the whole the African native shows a greater degree of immunity than the European intruder in the latter the disease tends to run a more acute course.

**Transmission**—This is effected by the agency of certain species of Glossina. This may be (i) direct or (ii) cyclical.

**Direct**—It has been shown that when a fly that is feeding on an infected animal is interrupted and then immediately allowed to feed on another uninfected animal the infection will be transferred to the second animal presumably by the contaminated mouth parts of the fly there is evidence that this occurs in nature and that during epidemic periods in particular infection is transferred from man to man by this means but it is also certain that the cyclical method of transmission is the usual one. Certain *Stomoxys* species are capable of transmitting the infection directly.

Cyclical—The fly takes the infected blood (figure 45, 1)

(1a) multiply and broader, lower free end this and the

multiply for some days, in this extra-peritrophic space they move anteriorly and reach the level of the proventriculus, where they penetrate the peritrophic membrane and reach the lumen of the proventriculus (2a) At this stage the trypanosomes are now all long slender forms, they continue to multiply, and still moving forwards they reach the opening of the salivary duct (2b) and eventually the salivary glands. In the salivary glands they continue to multiply, but undergo a further change of morphology becoming first crithidial (3) and then 'metacyclic' (4) forms short forms that are very similar to the short forms seen in the peripheral blood. The metacyclic forms are injected with the salivary gland secretion (4a) into the wound made by the tsetse fly's proboscis.

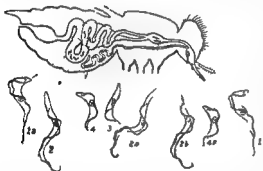


Figure 45 Diagrammatic outline showing position of different forms of trypanosome in the tsetse fly

- 1 Trypanosome form as found in the peripheral blood in the hypopharynx entering
- 1a Same form in the mid gut
- 2 Long slender form in the mid gut
- 2a Same form in the proventriculus
- 2b Same form in the hypopharynx on the way to the salivary glands
- 3 Crithidial form in the salivary glands
- 4 Metacyclic form in the salivary gland
- 4a Same form in the hypopharynx on the way out

The trypanosome loses its powers of infecting vertebrates soon after it reaches the mid-gut of the fly, but when it reaches the metacyclic stage it again becomes infective, the whole cycle takes from 10 to 25 days according to the circumstances temperature (optimum 75° to 85°F) being the most important factor

In only a proportion of flies—even of the recognized transmitting species—that feed on infected blood do the trypanosomes complete this cycle, but, when once infected, a tsetse fly remains infected indefinitely, the salivary infection being periodically replenished from the extra-peritrophic space. Newly hatched flies are more readily infected than older ones that have already taken a number of blood meals.

The infection is not transmitted hereditarily in the tsetse

Other possible means of transmission—A few cases of congenital infection have been reported and transmission is also said to occur during coitus

The tsetse fly vectors—There are four species of *Glossina* concerned in the transmission of sleeping sickness, *G. palpalis* and *G. tachinoides*, *G. morsitans* and *G. swynnertoni*, in nature the first two transmit the *gambiense* and the latter two the *rhodesiense* infections, though in the laboratory many other species have been shown to be capable of transmitting both infections

Flies of the genus *Glossina* (family Muscidae) are larger than *Stomoxys*, and have a similar type of proboscis, but a more hairy arista. The characteristic posture of the fly at rest is with wings folded scissor-wise, the wings show distinctive venation. They have a short stout proboscis, thick palpi with broad channels on their inner surfaces in which the proboscis lies (see figure 46 and plate I)



Figure 46 The tsetse fly  $\times 3$

compared to a coat sleeve lining that only reaches to the elbow where it ends free the upper end being sewn to the sleeve proper at the shoulder seam



Figure 47 Diagrammatic outline of mid gut of tsetse fly

The female fly does not lay eggs but gives birth periodically (about once a fortnight) to a larva (in girth nearly as big as the female itself) which it drops in a shady spot usually not far from water. This larva crawls into a place of safety and

immediately pupates. The pupa hatches into an adult after an interval varying from three weeks (at 85°F) to a month or two according to the environmental conditions.

Both male and female tsetse flies feed on vertebrate blood and flies of either sex are capable of transmitting trypanosomes. They feed almost exclusively during the day.

**Reservoirs of infection**—The role of wild game is a controversial subject. As far as the Gambian disease is concerned, it is generally believed that man is the sole source of infection and that game do not play an important part in the aetiology of this infection, many species of wild game, as well as domestic bovines and pigs, are potential carriers and one species of antelope has been found infected in nature by a trypanosome that appeared to be *T. gambiense*.

It is however fairly certain that wild game are the main source of infection for the tsetse fly.



Figure 48

infected with the latter trypanosome

#### EPIDEMIOLOGY

**Geographical distribution**—The disease is confined to tropical Africa between 15°N and 20°S

*Gambiense* infection extends from St Louis in Senegal, north of the Gambia river throughout all the countries on the west coast of Africa down as far as Angola but there are few endemic areas below  $10^{\circ}\text{S}$ . It extends as far east as Lake Tanganyika in the south, and further north into Uganda, and to the borders of the Anglo-Egyptian Sudan.

*Rhodnense* infection has a much more limited distribution, its realm is mainly in the south-east corner of tropical Africa, north, and in few areas south, of the Zambesi river, in Mozambique, Nyasaland, Rhodesia and Tanganyika.

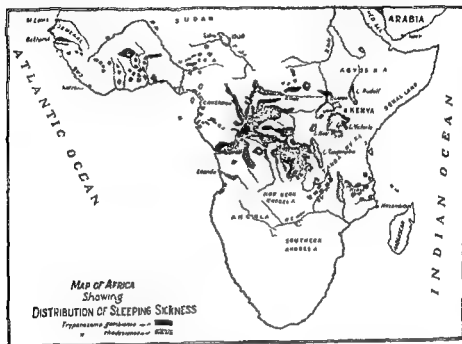


Figure 49

**Epidemic features**—The disease is in normal times endemic in the infected areas, but may become epidemic under special circumstances. These circumstances have mainly been associated with the opening up of the country and the migration of African natives into infected areas but in other cases the infection has undoubtedly been conveyed into new areas by the personnel of exploratory, commercial, scientific, and religious

an endemic area

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The relationship of the disease to wild game has been discussed above

**Local distribution**—In neither form of the disease is the whole  
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this fact

and moved their villages away from rivers and lakes but their need for  
water for themselves and their animals has necessitated their visiting water  
ing clearances where they are liable to get infected

**Effect of temperature**—The geographical distribution indicates that  
a moderately high temperature is essential and this observation has been  
supported by laboratory work. Kinghorn and Yorke (1912) showed that  
a temperature between 75° and 85°F was necessary for transmission

**Age sex race and occupation**—There are little differences in the age  
and sex susceptibility though men coming in contact with the infecting  
tsetse fly much more frequently are more liable to become infected how  
ever children who look after grazing herds of goats sheep etc during  
the hottest part of the day naturally rest in the shade and are very liable  
to be bitten by tsetse flies. There is also little evidence of any racial  
immunity though the inhabitants of the endemic areas suffer a more  
chronic form of the disease. Occupation is a very important factor boat  
men fishermen and others whose work takes them into closer contact with  
the tsetse are naturally more frequently infected

## PATHOLOGY

**Morbid anatomy**—When the parasite is injected it causes a local  
inflammatory reaction which subsides in a week or two the trypanosomes  
find their way into the blood stream and a septicæmia follows. The

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| | trabeculae  
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| | becomes  
sclerosed

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The 'morular' cell is a mulberry-shaped cell specifically associated with this disease, its origin is uncertain, but, as it is usually found in, or in close association with, nervous tissue, it has been suggested that it is a degenerated neuroglia cell, and, as it is also occasionally found elsewhere, it is thought that it may also originate from a plasma cell.

There are few changes in the nerve cells, except in the vicinity of the blood vessels, thus the pathological changes in the central nervous system are essentially interstitial and only secondarily parenchymatous.

The gross changes in the lymph glands are redness and swelling in the early stages and later become so hard that they come hard fibrous masses, in the posterior triangle, axillary, and mesenteric.

On opening the skull, the dura-mater may be found adherent, and there will be a generalized lepto-meningitis mainly confined to the vault and the inner surfaces of the hemispheres, there is an excess of cerebrospinal fluid, the brain is usually oedematous and the convolutions are flattened, the ventricles may be dilated, and on section a few areas of softening may be found into which hæmorrhages have taken place.

In other organs and tissues, there are few characteristic changes. The spleen is usually slightly enlarged, the liver soft and hyperæmic, there is sometimes a subacute nephrosis, myocardial changes have been described and are well developed in experimental trypanosomiasis in monkeys, and the bone marrow is hyperplastic.

**Cerebrospinal fluid**—This will be under normal or slightly raised pressure, 8 to 10 inches of water, and up 30 inches in exceptional cases. It is usually clear, and although when there is a high cell count it may be cloudy, definite turbidity suggests some bacterial infection.

The most constant change is the increase in the number of cells, and at first, most of the cells being lymphocytes, but the number steadily rises and other cells appear, large mononuclears, plasma cells, morular cells and possibly eosinophils. The count may mount to 2,000 per cmm or more, the cell count is apt to be very variable and is not as good a prognostic indicator as is the protein content.

Trypanosomes may be present but are not easily found, it will usually be necessary to centrifuge the fluid and examine the deposit. They are found in larger numbers in *rhodesiense* infections.

The most constant change is the increase in the protein content of the fluid. This may be 0.1 per cent or more, and is not subject to the same variations as the cell count in the parenchyma, whereas a high cell count only suggests inflammation of the meninges.

The changes in the cerebrospinal fluid appear very early in some cases, as early as three months from the first onset of clinical symptoms, they usually precede the development of symptoms referable to the central nervous system, and they are present in every case in which these symptoms are well developed.

The changes in the peripheral blood are not so constant in the peripheral blood. They are usually not so marked in *rhodesiense* infection, when they may

Anæmia is common in the later stages of the disease and the red cells have a tendency to clump when blood is taken for a red cell count which fact may make this a very difficult procedure. In the differential leucocyte count there is relative increase of large mononuclears.

In the urine albumin is often found early in the disease and it persists throughout otherwise no specific changes have been reported.

### SYMPTOMATOLOGY

It is convenient to divide the symptoms of sleeping sickness into two stages. The first stage of cerebrospinal involvement has survived from the time when the two syndromes were to be forgotten that the pathological process that produces both these sets of symptoms is a continuous one. There are in the first stage many signs and symptoms that suggest meningeal involvement and it is now well recognized that the characteristic changes found in the cerebrospinal fluid precede the development of the typical second stage symptoms by some weeks at least.

**Febrile stage.**—It must also be remembered that there are cases of entirely symptom free infection with *T. gambiense*. In a survey these symptom free infections may constitute the bulk of the infections identified and whilst a certain number of patients will develop cerebrospinal symptoms at a later date others undoubtedly remain symptom free for years if not for ever. This carrier state is more common amongst African natives but Europeans have been found infected during routine blood examination some years after leaving Africa.

Between these symptom free and the typical cases there are cases with all degrees of symptom development.

The typical case is described below —

The incubation period is not well defined it may apparently be as short as seven days though it is usually from two to three weeks before general symptoms appear.

The earliest symptom is the local reaction at the site of the bite of the infecting glossina. Normally the bite of the tsetse causes local pain followed in those not used to the bite by irritation that subsides in a day or two but in the local inhabitant it will often be unnoticed. The infected bite will cause a sharp local reaction that will usually be first noticed within seven days. A furuncle appears surrounded by an area of redness and induration this develops into a typical trypanosomal chancre a dark red raised button like lesion about an inch in circumference surrounded by an area of erythema and œdema it is very painful on pressure and it lasts two to three weeks. This primary lesion has recently attracted much attention as it is realized that it is the rule in European patients though less frequently reported by African natives that it provides an opportunity for early diagnosis as the trypanosomes are easily demonstrated in it and that it thus helps the institution of early treatment.

Fever may accompany this primary lesion or follow very shortly after its first appearance. There is sudden high fever which reaches 103°F or so within the first 48 hours high fever continues for about a week and then the temperature falls and remains normal or low for a few days before rising again for a few more days. After this the temperature





Fig 1—Romana sign (after Mazza)



Fig 2—Heart muscle showing *Trypanosoma cruzi* (trypomastix forms) (Conte)

which may lead to temporary paralyses of groups of muscles, and psychical disturbances mania and delusions, may occur

There is little change in the reflexes until almost the terminal stage, when the knee jerks, after a period of over brisk response, may be absent and the sphincter controls lost. The pupils usually react normally.

Optic atrophy has been described, even in the absence of any arsenical treatment, and there may be œdema of the disc due to meningeal involvement, with or without increased intracerebral pressure.

This stage seldom lasts more than a year if no treatment is given though there have been instances of temporary remission with consequently a much longer duration. In more severe cases the end will come within three or four months. Death in convulsions has been reported, but the usual termination is from emaciation and complications, *e.g.* bed sores, bladder infection, pneumonia, etc.

### DIAGNOSIS

The common clinical signs and symptoms of the early stages are the trypanosome 'chancre', irregular fever, glandular enlargement—particularly in the neck, the rash, and Kerandel's sign, but it will always be advisable to confirm the diagnosis by finding the trypanosome.

Certain presumptive laboratory tests will be of value only in cases in which the clinical signs are not characteristic because in a typical case they add little weight to the provisional diagnosis, and parasitological confirmation will still be necessary.

To carry out a survey in an endemic area after a preliminary selection of suspected cases by gland palpation thick film examination, gland puncture and lumbar puncture should be done.

In the later stages, the parasites in the blood are very scanty and the glands may be sclerosed. In these cases the cerebrospinal fluid will be the only medium of diagnosis, even in the absence of trypanosomes, which are always difficult to find. Characteristic changes in this fluid are considered to be diagnostic.

The confirmatory and presumptive methods of diagnosis can be summarized as follows :—

**Confirmatory methods.**—(i) Direct examination of fluid from the primary lesion (trypanosome chancre).

(ii) Gland puncture

(iii) Examination of the peripheral blood, (a) direct coverslip examination, (b) by the thick-film method, and (c) after triple centrifugalization.

(iv) Lumbar puncture.

(v) Animal inoculation

**Technique**—(i) The indurated margin of the lesion is pricked with a needle and the fluid that exudes is examined under a coverslip, or a smear is made, stained by Giemsa's method, and examined

(ii) The skin over the gland to be punctured is sterilised, and the gland is held firmly with the left hand while a hypodermic needle of wide bore is thrust into it. The needle is moved backwards and forwards a several centimetres

(iii) (a) A drop of blood taken from the finger or ear-lobe is mixed with an equal quantity of citrate saline and examined under a vaseline-ringed coverslip with a 1/6 inch objective, the attention will be drawn to the trypanosome by the movement of the red cells

(b) the thick-film methods of examining for malaria parasites (see p 87) can be utilized, Field's rapid-staining method gives excellent results

(c) About 5 ccm of blood is withdrawn, placed in a centrifuge tube containing 1 ccm of 2 per cent sodium citrate solution, and centrifuged at low speed. This will throw down the majority and centrifuged again at the the leucocytes are deposited. A third time at a rapid speed now examined, directly under

... can be obtained by either lumbar or cisternal puncture. The fluid can be examined by either of the methods mentioned above.

**THE EVILS**

Pandy's test is a simple and most useful test to carry out in the field. One part of the fluid is mixed with 9 parts of 2 per cent sodium citrate solution (1 part of the fluid to 9 parts of the solution).

**nervous system**

(v) Of laboratory animals, mice, rats, guinea-pigs and rabbits are all susceptible to infection, and strains can be maintained for long periods by passage through these animals, but to establish a strain in the laboratory, it is usually necessary to make the first passage through a monkey, *Sûenus rhesus* or some other monkey. The amount of 5 ccm of citrated triple-centrifugalized blood is used in the same way.

A differential diagnosis between *T. gambiense* and *T. rhodesiense* can be satisfactorily made only by animal inoculation; in the latter, the

infection is much more virulent, and posterior-nuclear forms will appear (*vide supra*).

When blood is examined constantly, it should at once arouse suspicion, so that the gland juice can be examined for a longer period than usual before being pronounced negative.

(ii) Brown's adhesion phenomenon depends on the fact that, in the presence of immune serum, platelets and other small particles (*e.g.* bacilli) will adhere to trypanosomes, it is claimed that the test is species-specific.

(iii) The serum-formalin test is carried out in the same way as for kala-azar (see p 164).

The 'positive' result is not as clear-cut as in kala-azar, though a definite change occurs in all advanced cases of sleeping sickness, and many other conditions produce confusing results, so that it is not a test of great value in the human disease, ■ it is in animal trypanosomiasis, *e.g.* camel trypanosomiasis in which it is the routine diagnostic procedure.

## TREATMENT

**Historical.**—From the earliest days, arsenic in one form or another has been used in the treatment of sleeping sickness.

In 1910

In 1908 Plummer and Thomson showed that intravenous sodium antimonyl tartrate caused trypanosomes to disappear from the blood of experimental animals, Kerandel claimed ■ have cured himself with potassium antimonyl tartrate after atoxyl had failed.

Many other arsenical antimonyl preparations were introduced and tried, but none had the same effect as atoxyl.

propane are believed from more limited experience to be superior. It was again at the Liverpool School of Tropical Medicine by Yorke (1940) and his co-workers that this group of drugs was introduced.

An 'incident' in the history of the treatment of sleeping sickness was the wide publicity given in the early inter-war period to the now finally discarded salvarsanized serum treatment.

Specific drugs and dosages.—At the present day, the only specific drugs that have survived an extensive trial are—atoxyl, which ■ now

practically obsolete, orsanine, and germanin (or antrypol, a British product which is identical with germanin\*), for treatment in the first stage and tryparsamide for the meningo-encephalitic stage, orsanine is also used in the latter stage but its value is very limited. The antimonials may be looked upon as an adjuvant treatment in arsenic-resistant cases. The aromatic diamidines show considerable promise, but have not yet undergone the test of time.

**Atoxyl** is given in a 10 per cent solution in sterile distilled water, in doses of 10 mg. per kilogramme body-weight, weekly for six to eight weeks. Side-effects can be expected, but

are usually tramucularly, or intravenously in water, in doses of 20 to 35 mg. per kilogramme individual dose. Injections are given weekly for ten to twelve weeks. It is less toxic and more efficient than atoxyl in sterilizing the peripheral blood in the early stages, but it is far less efficient than tryparsamide in the meningo-encephalitic stage, though it is still used in this stage.

**Tryparsamide** is given intravenously in a 20 to 40 per cent solution in sterile distilled water, in doses of 20 to 40 mg. per kilogramme body-weight, up to a maximum individual dose of 3 grammes in an adult, at weekly intervals for 10 weeks. Chesterman recommends larger doses, of the order of 60 mg. per kilogramme in adults, with a maximum of 4 grammes for an individual dose. This drug has a relatively poor trypanocidal action and is therefore not given in the early stages, but it appears to possess special powers of penetrating nervous tissues, and is therefore the drug of choice in the late stages of the disease.

**Antrypol or germanin** is given intravenously in a 10 per cent solution in sterile normal saline, in doses of a gramme for an adult twice or thrice weekly, up to a total dose of 10 grammes.

**4,4-diamidino diphenyl ethylene diphenoxy pentane**, and diphenoxy propane, the members of the diamidine group that have so far been used are given in a 2 per cent solution in sterile distilled water, in doses of 1 mg. per kilogramme body-weight thrice weekly, up to 15 injections.

**Antimony preparations**—Sodium antimonyl tartrate has been largely superseded by other less toxic drugs. The trivalent foudin and the pentavalent neostibosan have been used with some success and are given in the dosages used in leishmaniasis (see p. 168).

**Toxic effects**—All the pentavalent arsenical drugs may give rise to toxic symptoms even when given in moderate doses, but the likelihood of this occurring increases with the dose. Each drug has its own specific range of toxicity, and individual susceptibility is a variable factor.

Occasionally, severe diarrhoea and vomiting will occur, liver disturbances and dermatitis are rarer than with the trivalent arsenicals, but do occur. Visual disturbances are usually the limiting factor, these may be serious. The earliest symptoms are dimness of vision, contraction of the visual field and sometimes flickerings. Later, blind spots will appear and eventually there will be complete blindness.

\* A French product moranyl (Fournieu 309) is also identical with germanin.

Little change will be seen by use of the ophthalmoscope until permanent and irreparable damage is done. Therefore a patient having tryparsamide should if practicable have his vision tested before the course is started, and then before *each* subsequent dose, if there is any deterioration of vision the tryparsamide should be stopped immediately. If this is done directly the early symptoms appear, the vision will usually improve again.

Optic atrophy is more likely to occur in advanced second-stage cases than in early cases, and is due both to the disease—which alone will occasionally produce it—and to the treatment.

When one is treating uneducated African natives it will be impossible to test their vision accurately and one has to face the fact that in a certain proportion of cases blindness will occur and to hope that if treatment is stopped immediately they will recover.

Certain alarming, both early and late, toxic effects from 4, 4'-diamidino diphenyl ethylene have recently been reported.

The treatment of the case.—Early institution of treatment is very important as the trypanosome is very much more easily killed before it has established itself in the meninges and brain. The *gambiense* infection is much more amenable to treatment than the *rhodesiense*, which is very apt to become arsenic-fast.

In the first stage of either infection, antrypol is the drug of choice, but in *gambiense* infection orsanine may be used as an alternative. Yorke considers that the danger of making a *rhodesiense* case arsenic-resistant should deter one from using any arsenic drug in the early stages.

In the meningo encephalitic stage, tryparsamide is the only really satisfactory drug. Orsanine will undoubtedly produce cures in this stage, and claims as high as 50 per cent have been made for it, but it is generally agreed that it is inferior to tryparsamide.

When once changes have occurred in the meninges, the physician must resort to antimony preparations, and to antrypol, though the latter is only useful when once changes have occurred in the meninges.

The art of the treatment in this disease resolves itself into striking a balance between the toxic and the efficient dose of the trypanocidal drugs, and playing them in such a way that the infection does not become drug-resistant—this drug resistance is not confined to the arsenic compounds. Inadequate dosage certainly tends to produce drug-resistance. Chesterman



injections of some arsenical compound e.g. orsanine. Cure is not effected but temporary sterilization or at any rate a marked reduction in the

possible wild game reservoir of *rhodesiense* infection opens up controversial subjects which it would be out of place to raise here

(u) The tsetse fly — *G. palpalis* remains near the shores of lakes and

of bush (Symes and Southby 1938). Trapping and other special methods have been introduced in special circumstances

apparent success

Rules have from time to time been put into operation to prevent migration of susceptible natives into infected areas but are difficult to enforce

(iv) Contact between the tsetse and man — As the tsetse bites during the day it is difficult to devise means of protection. Clothing certainly helps to protect the European sojourner. Night travel has in the past been resorted to in order to avoid infection

The location of settlements away from rivers and lakes and the aggregation of the population into relatively large villages as opposed to wide distribution in scattered homesteads are measures that are now being adopted. It is possible to make wide clearings around these villages and of course this should be extended to the roads as far as possible

Gibbins (1941) has recently investigated the use of rod shaped clearings along streams watering places and road crossings. These clearings discourage *G. palpalis* from lingering to bite man

As in the case of almost every tropical disease the economic agricultural and nutritional aspects of control loom large and the subject has to be studied from all these points of view

#### PROGNOSIS

Untreated *gambiense* infection may run a very chronic course of some years duration whereas *rhodesiense* infection usually runs a rapid course of a few months duration but there are exceptions in each instance

Prognosis in the treated case will depend on the stage at which the diagnosis is made and treatment instituted on the species of infecting

the prognosis is usually much graver



To this general rule there are exceptions, some strains of *T. gambiense* are very resistant to treatment, and there are strains of *T. rhodesiense* that respond readily

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# CHAGAS'S DISEASE, OR SOUTH AMERICAN TRYPANOSOMIASIS

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**Definition**—South American trypanosomiasis or Chagas's disease is usually acute in its early stages and is characterized by local swellings, fever, adenitis and anæmia, and later develops varied chronic manifestations, cardiac, nervous or myxodematous; it mainly affects children and it occurs in South and Central America. It is caused by *Trypanosoma cruzi*, which is transmitted to man by reduviid bugs of the family Triatomidae, notably *Triatoma megista* and *Triatoma infestans*.

**Historical**—The history of this disease is almost unique in that the causal organism and the mode of transmission were discovered in the laboratory before

## ÆTIOLOGY

**The causal organism**—This is now classed as a trypanosome, but in view of certain differences between it and other trypanosomes, it was at one time placed in a separate genus, *Schizotrypanum*

**Morphology and staining**—It has two forms, a flagellate form in the transmitting insect and in the blood of the vertebrate host, and a leishmania form in the solid tissues of the latter. The flagellate form passes through various developmental stages, appearing as a trypanosome, a crithidia, and a leptomonas in the insect vector, and also probably in the vertebrate hosts' tissues

In the blood, only trypanosome forms are seen, these may be either short stumpy or long slender forms. In their morphology and staining, they differ very little from the trypanosomes of the African disease (qv), but they are slightly larger, measuring about  $20\mu$  as a rule. The stained specimen assumes a characteristic C shape (see plate B)

When they invade the host cells, they lose their undulating membrane and flagellum, and become leishmania forms (see KALA-AZAR),  $1\frac{1}{2}$  to  $4\mu$  in diameter. They multiply rapidly by binary fission and destroy the host cell which eventually bursts, when they may find their way into other cells, or back into the lymphatic fluid and blood, but it is only trypanosome forms that are seen in the latter

**Distribution in the human host**—As noted above, the trypanosome forms are found in the blood, though in the human host they are very scanty in the peripheral blood. The leishmania forms are found mainly in the endothelial cells of the capillaries and lymphatics, and in the heart muscle, but they also invade the cells of the skeletal muscles. They thus occur in nearly all the organs and tissues of the body, spleen, liver, suprarenals, ovaries, testes, thyroid, brain, bone marrow, mucous membranes, and subcutaneous tissue. They have also been found in the cells of the epidermis

**Transmission**—There are many potential vectors but, as far as is known at the present time, two species are mainly responsible for the transmission of the disease to man, namely *Triatoma megista* and *Triatoma infestans*. In the endemic areas these bugs are repeatedly found infected in nature, sometimes to the extent of 90 per cent of specimens examined. They have also been found infected in countries where few or no cases have been discovered, e.g. in Mexico, where recently a very few cases have been reported, and in California, Texas, and Arizona, where no case has yet been found. Further, a trypanosome, apparently identical with *T. cruzi*, has been found in nature in a large number, at least twenty, of species of *Triatomidae* and many of these have been shown experimentally to be potential vectors

Other arthropods, e.g. *Cimex*, *Ornithodoros*, *Rhipicephalus*, have also been shown to be capable of maintaining the trypanosome in their intestinal canals, and of transmitting it

The infection is said to be transmitted from the adult bugs to their progeny in the ovum, but it is more likely that the larvae are infected by the faeces of adults

**Mechanism of transmission**—The bug becomes infective eight to ten days after feeding, at any nymphal stage or in the adult stage, on an infected vertebrate, and retains the infection for the rest of its life, up to

two years. The trypanosome multiplies and passes through different developmental stages to become a metacyclic, short stumpy, form which is passed in the faeces. The salivary glands are affected by but by the assed in the the wound

made during the bite, and possibly by contamination of the conjunctivæ with the fingers. The irritation caused by the bite will lead to scratching, so that either of these events is a likely sequel



Figure 30 *Triatoma megista*

opossum

Domestic animals are also found naturally infected, as the cat and the dog, in a high percentage. It seems probable that wild animals are the main sources of infection, as triatoma have been found living in their burrows.

Cats and dogs are infected by feeding on infected rodents.

#### EPIDEMIOLOGY

**Geographical distribution**—All the earliest cases were reported from the Minas Geraes district of Brazil, and in fact, as pointed out by Yorke (1937), only a little over a hundred cases had been reported from anywhere else up to that date, despite the very wide distribution of the infection in animals and of the potential insect vectors. However, during the last few years more cases have been reported from many South American countries: Argentina, Uruguay, Peru, Venezuela, and Chile from Panama, Guatemala and San Salvador, in Central America and recently from Mexico.

No human case has yet been reported from the United States.

After Brazil, Argentina has provided the largest number of cases, and this had reached about 500 by 1940 (Marza). In most other countries only isolated cases have been found even after systematic investigation.

**Epidemic features**—The disease is sporadic and occurs mainly amongst the infants and young children of the lower classes in the endemic areas. Children of either sex are attacked and usually the first symptoms appear before they are two years old. Older children and adults are occasionally affected. The disease is commoner in country districts than in towns.



Figure 51

### PATHOLOGY

The type of lesion that is produced by the parasite is fairly constant, but the distribution amongst the organs and tissues of the body is very variable, this accounts for the diversity of the clinical manifestations

Cells in different parts of the body, mainly endothelial cells of the capillaries and lymphatics, and the reticular cells of other organs and tissues, are invaded, multiply, and form cysts. This occurs in other organs and tissues

There appears to be an early brisk tissue reaction during the period of invasion, e.g. in the heart in a child who died within a few weeks of the first symptoms, there was an invasion of histiocytes and monocytes in the reticular tissue between the heart muscle fibres, but parasites were so scanty that only one or two were discovered, later, however, the local response to invasion appears to be very slight and large cyst-like bodies containing numerous multiplying leishmania forms are seen, with very slight reaction beyond a little fibrosis occurring in the surrounding tissues

The organs affected are mainly the heart, the brain, the suprarenals, ovaries and testes, the thyroid, the lymphatic glands, and the liver. The parasite also has a predilection for skeletal muscles

Most of the chronic changes described have been in the thyroid, but it now seems very doubtful if these are really due to the trypanosome infection (*vide infra*)

In the heart, interstitial fibrosis of the myocardium, with parasites still present in a few cases only, is probably the commonest chronic lesion

### SYMPTOMATOLOGY

As in most other infections by parasites of the family Trypanosomidae the reaction to the infection is very variable, and it seems certain that many infections do not reach the clinical threshold. In the few experimental infections the symptoms have usually been mild and temporary

An early acute and later chronic form of the disease are recognized

In the acute form which is nearly always in children, after an incubation period of 10 to 20 days, there is a sharp febrile attack of moderate intensity which lasts for about three weeks. At the beginning of this attack, oedema of one side of the face may occur. This oedema may spread to the neck, shoulders, chest, and arms, and in a few cases general anasarca has been reported. This unilateral swelling of the face, which is usually most noticeable in the loose cellular tissue of the eyelids, is known as Romana's sign. The unilateral nature of this sign suggests that it is in some way associated with the original point of entry of the infection, at the site of the bite, or via the conjunctiva, it does not appear to be the immediate reaction to the bite, but rather of the nature of a later allergic reaction when the general infection is established. There is often a morbilliform rash on the arms and trunk

Other accompaniments of the acute attack are dyspnoea, cyanosis and other acute cardiac and cerebral symptoms. The liver is often enlarged, and the lymphatic glands in the neck and other parts of the body are enlarged. In a child

the + the chagoma form there a considerable amount of the lesion.

..

If this view is accepted, there is little left of the chronic syndrome. The patients who have been found infected, often accidentally and/or at post mortem, have shown a variety of symptoms, but the most commonly recurring ones are those associated with a chronic form of heart disease, with alterations in conductivity and disturbances in rhythm.

Early death from chronic fibrotic changes in the heart is common in the districts where infected bugs are found, and, in the absence of any other obvious cause for this, and in view of the facts that many of these persons have been shown to be infected and that this trypanosome undoubtedly has a predilection for heart muscle, it is tempting to associate these two observations.

**Chagomas**—This term has been introduced recently by Mazza to

..

after the primary lesion. The inoculation chagoma appears within about a week of the inoculation and persists for some weeks, and leishmania forms of the parasite can be found in it.

### DIAGNOSIS

The clinical diagnosis in a typical case does not present any particular difficulties. Romana's sign in children and the more recently described chagomas in both adults and children will arouse strong suspicion. During the first few weeks of the infection, confirmation is not usually difficult, in a large percentage of cases, trypanosomes can be found in the blood, by direct examination or by the triple centrifugalization method (see p 210). The leishmania forms can also be demonstrated in the chagomas.

Later, animal inoculation or xeno-diagnosis will be necessary.

For the former, young animals, guinea-pigs or better still puppies, are inoculated with the deposit after triple centrifugalization of 10 cm of blood from the patient. After about 14 days, the trypanosomes will be found in the blood of the animal.

Xeno-diagnosis is carried out by a laboratory-bred triatoma to feed on a suspecting the bug and demonstrating it. considered too elaborate a procedure for out, as a long-established laboratory strain of triatoma must be used in order to obviate a false positive finding.

The Machado-Guerrero reaction is a form of complement-fixation test, in which an extract made from a heavily infected puppy's liver is used as antigen. A more recent modification is to prepare a more standardized antigen from cultures of *T. cruzi* in blood dextrose agar. The test is said to be specific to a high degree at any stage after the early acute stage, it is not usually positive before the 30th day. The result may however be positive in sleeping sickness and kala azar, the latter disease occurs in South America. Both complement fixation and slide agglutination tests have been used and apparently give accurate results.

### PROGNOSIS

A high death rate is reported in the early acute stage in young children, the death rate is usually placed at about 50 per cent in the first year of life. It must be remembered that the disease is often accompanied by ulcers and adults, for example, have been shown to be suffering from a chronic infection.

### PREVENTION

The dark corners and the thatched roofs of the huts of the poor obviously are favorable for the development of the disease, therefore any measure to improve the living conditions upon as a preventive procedure that mosquito nets, even if they are not used, should certainly be so protected.

### TREATMENT

None of the drugs so far used in the treatment of sleeping sickness has been of the slightest use in Chagas's disease.

Mazza has reported very good results with Bayer 7602, a preparation of 1,6-dimethyl-2,4-diaminopyrimidin-4-ol, given intravenously in a solution in 5 per cent glucose solution. Brumpt has been successful.

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## THE RELAPSING FEVERS

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**Definition**—Relapsing fever is an acute specific disease occurring in many parts of the world, characterized by fever that appears in bouts of a few days' duration, with a sudden onset a rapid subsidence, and a tendency to relapse at regular short intervals, it is caused by a spirochæte that is found in the blood and in other organs and tissues, and is transmitted to man by insects of at least two genera. The symptoms vary with the genus of the transmitting insect.

**Discussion.**—Relapsing fevers that comply with the above definition have been described in many temperate sub-tropical and tropical countries. The causal organism is not identical from one another but have been generic and specific by various workers —

Generic name	Specific name	Location	Insect vector
<i>Spirochæta</i> <i>Spironema</i> <i>Treponema</i> <i>Borrelia</i>	<i>recurrentis</i>	Europe	<i>Pediculus humanus</i>
	<i>obermeyeræ</i>	Europe	
	<i>carleri</i>	India	
	<i>novyi</i>	America	
	<i>egyptica</i> (um)	Egypt	
	<i>berberis</i> (um)	North Africa	
	<i>duttoni</i>	Central Africa	<i>Ornithodoros moubata</i>
	<i>rossi</i>	East Africa	
	<i>kochi</i>	East Africa	<i>O. savignyi</i>
	<i>crocidura</i>	Africa	<i>O. lahorensis</i>
	<i>persica</i> (um)	Peru and N W Africa	<i>O. papillipes</i>
	<i>sogdiana</i> (um)	North Africa	<i>O. moubata savignyi</i> and <i>erraticus</i>
	<i>marocana</i> (um)	Morocco	<i>O. moubata</i> and <i>savignyi</i>
	<i>hispanica</i> (um)	S Spain	<i>O. maroccanus</i>
	<i>neotropicæ</i>	Panama	<i>O. talje</i>
	<i>venezuelensis</i> (e)	Venezuela and Columbia	<i>O. venezuelensis</i>
	<i>turicata</i>	Texas	<i>O. turicata</i>
	<i>normandi</i>	North Africa	<i>O. moubata savignyi</i> and <i>erraticus</i>

The confusion in the generic names is due to natural conservatism on the part of the clinician, which is not surprising in the circumstances, and to disagreement on the part of the parasitologist, mainly on the issue of priority, there is no suggestion that there is more than one genus concerned

The result of of course is that the "hand" carries with it ent species in each of justification for any there are two species concerned, *Spirochata recurrentis* and *Spirochata duttoni*, which are the causal organisms of the louse-transmitted and the tick-transmitted relapsing fevers, respectively, and that all the other names are synonyms: *obermeieri*, *carteri*, *berbera*, *egyptica* and *noyi* for *recurrentis* and the rest for *duttoni*. As well as their morphology the two organisms have other common features but there are many differences that seem to justify their distinction into two separate species. In the clinical syndromes as well as in the epidemiologies of the respective infections produced by the spirochaetes of these two species there are marked differences and they will be described separately



Figure 52  
*Treponema  
recurrentis*

## LOUSE BORNE RELAPSING FEVER

**Historical**—Rutty is given the credit for the first description of the disease epidemic—and probably later—natural as the two diseases old bilious remittent malaria. Since this date there have been many epidemics in association with louse-borne relapsing fever.

## EPIDEMIOLOGY

**Geographical distribution**—Relapsing fever has occurred in epidemic form at some time or other in almost every country in the world. During the last twenty years or so, it has occurred in eastern Europe—Poland, Russia, and the Balkans—in Africa—in two belts divided by the Sahara desert, north Africa from Morocco to Egypt and central Africa from Senegal to Abyssinia, and in Asia—Turkey, Syria, Iraq, India (except Bengal and Assam), China and Indo China, Mongolia, and Asiatic Russia.

It seems probable that it does not occur in Australia or in the East Indies. Western Europe, with the exception of Ireland has been free for some years, and no recent outbreak in America has been identified as louse-borne.

**Epidemic features**—It is essentially an epidemic disease but cases that are apparently sporadic occur from time to time. Like most epidemic diseases it tends to occur in cycles, in this case the cycle has a 15 to 20-year periodicity. But it is certain that unnatural events such as wars, persecutions, poverty, and destitution, assist the natural events that determine the onset of the epidemics, e.g. the epidemic in eastern Europe and western Asia during and after the 1914-18 war.

Any country where the habits of the people are not naturally cleanly or where overcrowding and/or destitution are common is likely to suffer

epidemic outbreaks, and the disease is liable to spread to, and in, other countries and communities when normal standards are not maintained, during wars—amongst both troops and refugees—famines, and earthquakes and other natural disasters

A severe epidemic occurred in the African epidemic belt south of the Sahara (*vide supra*) from 1921 for about eight years, and affected some millions of persons, the death rate is said to have been about 5 per cent of the populations of these countries, and in some it was as high as 25 per cent. In India, there has been little relapsing fever since 1929 when the last traces of the 1923-4-5 epidemic disappeared

Epidemic relapsing fever is very frequently but not only always associated with epidemic typhus, in a mixed epidemic the latter usually predominates

Seasonal incidence—There is a distinct seasonal variation in incidence, the height of the epidemic wave is usually in the spring. In India and Iraq, the disease used to disappear completely during the hottest months of the year

Age sex race, and occupation—Relapsing fever appears to be most common in male adults, but persons of all ages and both sexes are susceptible. Individuals of all races are susceptible unless protected by previous experience of the disease when a large percentage of the population is thus protected, racial immunity may be simulated

Washermen or -women, and dealers in old clothes are particularly liable to be infected. Nurses and hospital attendants are also exposed, but not doctors, at least spirochaetes are not present  
no air borne infection

### ÆTIOLOGY

Historical—Obermeier first found the parasite in 1868 but he did not describe it until about five years later. Lebert named it *Protomycetum recurrentis* in 1873, but later the specific name *recurrentis* was given to the organism by Vandyke Carter in 1891. In India, his observations were confirmed and extended by Nicolle, Blaisot and Conseil (1913) in north Africa who showed that the transmission was not by the bite but by the crushing of the louse on the skin. The spirochaete and gave it different names, but the important transmitter was the louse.

The causal organism Morphology and staining—*Spirochaeta recurrentis* is an actively motile spiral organism with five to ten fairly regular loose primary spirals, it is from 10 to 20  $\mu$  in length and about 0.2  $\mu$  in thickness, each spiral is 2 to 3  $\mu$  in length and 1  $\mu$  in amplitude. The spirochaetes can be seen, though not accurately, in a fresh specimen of blood preferably by dark-ground illumination. They move by rapid

\* The generic name *Spirochaeta* is used here because it is still the most popular one.

peritrematous, an organism with regular short spirals (morphologically indistinguishable from the causal organism of syphilis) the cause of yaws *Treponema caraleum*.

rotation but not apparently purposefully for they move backwards and forwards within the space of the microscopic field

**Culture**—The spirochaetes can be grown anaerobically in a medium containing ascitic fluid citrated blood and kidney substance but they do not grow well

**Distribution and pathogenesis**—They are found in the blood during the height of the febrile attack but disappear just before the fall of the temperature reappearing during the relapse It has been suggested that  
tion  
the  
etes  
the

spleen and the brain where they can be found as such

Infection can be transmitted to a number of animals *eg* monkeys squirrels rats and mice but not to rabbits or guinea pigs In monkeys  
S  
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I

less constant

n attack they  
irochaetes and  
not last long  
very complete  
the antigenic  
es they are in

of a much lower order than that between the various strains (or types) of *recurrentis* (*vide infra*)

body  
the  
they  
and  
antibody load is sufficient to knock out the infection altogether  
that the immune  
to disappear into  
isitory and when  
blood multiply  
so on until the

In the writer's opinion the more feasible explanation is that there is a multiplicity of strains with slightly differing antigenic structures (*cf* the antigenic structure of Flexner dysentery strains *q v*) that when a person is infected he is infected by a number of strains of which one is dominant and causes the first bout of fever antibodies appear and suppress the spirochaetes of this first strain spirochaetes of another strain, hitherto dormant now appear and multiply and so on until eventually enough antibodies are formed to counteract spirochaetes with all possible antigenic patterns This hypothesis is supported by the work of Cunningham and others (1934 *et seq*) in which he showed that in one individual the 'type' of spirochaete present in the initial attack was different from that present in the first relapse and that when a second relapse occurred a third type appeared and so on The type recoverable during the apyrexial period was always the type that appeared in the next paroxysm He separated

nine antigenic types (as he called them) four of which were stable types maintaining their antigenic individuality through many sub passages but the other five tended eventually to revert to one or other of the four stable types

**Transmission**—This is effected by the louse *Pediculus humanus*. After the louse has fed on an infected person the spirochaetes disappear in about 24 hours and are not traceable in the louse nor is it infective for another three to five days, after this they reappear as slender metacyclic forms in the fluid of the body cavity of the louse and can be found in all parts of its body (they are easily demonstrated by taking off a leg and making a smear from the exuding fluid) the louse remains infective for the rest of its life. Transmission occurs when the louse is crushed and the body cavity fluid rubbed into the abraded skin. The bite of the louse does not transmit infection nor do its faeces. It is a question whether infection can be transmitted through the unbroken skin by the blood or

**Source and spread of infection**—Whilst man is not the only susceptible on man so that man must

spirochaetes of endemic relapsing fever (*vide infra*) might provide the initial infection for a louse borne epidemic. It has been shown that it is possible to infect lice with this organism and it is conceivable that after several passages through the louse the spirochaetal strain might undergo some biological change so that it behaves like or actually becomes *Spirochæta recurrentis*. The infection is spread by direct contact with the body of a louse infected patient by handling his louse infected clothes or by louse interchange during close contact and it may be conveyed considerable distances in louse infected clothes

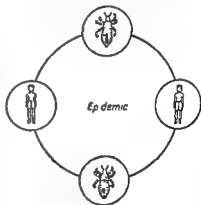


Figure 53 The transmission cycle in louse borne relapsing fever

### **PATHOLOGY**

**Morbid anatomy**—The large majority of the patients who die from this condition die from some secondary infection and the true pathological picture is hard to gather

jaun  
spleen

and mucous membranes are  
emorrhages The liver and

The most constant lesions are in the spleen this organ is enlarged and soft and shows many milium necrotic lesions especially in the

areas of congestion and cell infiltration  
which spirochaetes will be found inside

In the bone marrow there is marked leucoblastic hyperplasia

In the other organs, in the liver and kidney, there is cloudy swelling and degeneration of the parenchyma cells

**Blood picture**—There is usually a distinct polymorphonuclear leucocytosis, with an actual increase in large mononuclears also. Counts of about 12 000 to 15 000 per c mm are usually found. This is not a constant finding.

Reference to the presence of the spirochæte in the blood has been made above (see also Diagnosis)

**Urine**—Slight albuminuria will be found in more than half of the cases, and often granular casts, in severe cases there may be hæmaturia

### SYMPTOMATOLOGY

The incubation period is from three to seven days as a rule, the limits being from 2 to 14 days. (In experimental infections it has always been between two and six days)

temperature rising to  
are often severe  
particularly severe  
The skin is hot  
The eyes show  
red but usually  
the onset is not

unusual and may be a marked feature of some severe epidemics

An erythematous rash appears early in the first febrile attack in perhaps less than half the cases. In severe cases this may become petechial and even hæmorrhagic. It appears to start from the tip of the mastoid process and it spreads out over the neck, shoulders, arms, back and chest.

Frank jaundice occurs in 20 to 50 per cent of cases in different epidemics; it appears early.

Both spleen and liver are enlarged in the majority of cases, the latter will usually be tender. The splenic enlargement is only slight and may disappear between attacks. The first attack usually lasts five or six days but occasionally it will be prolonged even up to 12 days; the crisis then occurs and the patient's temperature drops to sub normal with profuse sweating and in severe cases with considerable prostration. Heart failure at this stage is not uncommon. Cases have been reported in which the temperature fell 10°F in a few hours.

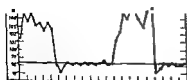


Figure 51. Temperature chart in louse-borne relapsing fever (original)

of the first attack to the onset of the first relapse is constant for each type of relapse, as in 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

days, average 13 days. This view

The first relapse is seldom as severe or as long as the initial attack but is otherwise very similar to it. After another interval usually shorter than the first, in the writer's experience there may be a second relapse which will again be shorter and less severe than the first.

In this form of the disease there are never more than four relapses. The following figures have been given for the number of relapses that occur in different epidemics —

A single attack	10 to 50 per cent
One relapse	25 to 50
Two relapses	10 to 40
More than two relapses	1 to 2

**Complications and sequelæ** — Cough and bronchitis are so common in temperate climates that they may be looked upon as a constant feature of the disease. They are less common in the tropics. Broncho pneumonia is a relatively common complication in cold climates.

In pregnant women abortion will usually occur. Eye complications are not uncommon particularly in a mal nourished population these include iritis and ophthalmia.

Parotitis, nephritis, polyarthritis and neuritis are rarer sequelæ the latter is very rare in this form of the disease though common in tick borne relapsing fever.

### DIAGNOSIS

While the complete temperature chart of a case of relapsing fever is so characteristic that one could scarcely fail to recognize it it must be

In most epidemics the parasites are easy to find but are easily overlooked if not specifically looked for.

Giemsa's or Leishman's stains will show up the spirochaetes very well. In looking for malaria parasites one focuses on the red cells and not between them so that unless one expects to find spirochaetes it is very easy to miss them even in a well stained film. The curious circular form that they may take simulates a rather pale red cell but if one examines these forms carefully the disguise is easily penetrated.

It should be remembered that the spirochaetes disappear from the peripheral blood 24 hours before the crisis. They will not be found during the remission period and are usually scantier in a relapse than in the initial attack.

**Differential diagnosis** — At the height of the attack influenza, dengue, even small pox may be mistaken for dengue usually very slow.

### PREVENTION

Preventive measures will consist in keeping the populations in a louse free condition in preventing conditions that will encourage an interchange of lice (e.g. overcrowding) in the early hospitalization and treatment of all cases and in instituting special measures for delousing all patients admitted to hospital during an epidemic.

Established lousiness will never be tolerated by an educated and sane individual, in ordinary circumstances, and its prevention is solely a matter of personal cleanliness.

The clothing of hospital and ambulance personnel should be white, one-piece, and with no openings in front (figure 55), gloves and gum-boots should be worn and the sleeves and trousers tied firmly round the wrists and ankles, a white handkerchief tied round the head, covering the hair, and a gauze mask worn across the mouth and nose. For

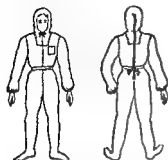


Figure 55 Figure shows one piece suit for use by hospital and ambulance personnel. It is closed by means of a zipper behind elastic round the wrists and a tape round the face tied under the chin.

where typhus is also suspected. For hospital personnel the best protection that can be given is the complete delousing of the patients before admission.

head, followed by thorough washing with antiseptic soap under supervision. Women will usually object to having their heads shaved and an elaborate process of hair washing is necessary.

mixture is —

Kerosene	50 per cent	Citronella oil	1 per cent
Tar oil	5	Coconut oil	44

Coconut oil alone will not destroy lice though it may gum up the ova and prevent hatching to some extent.

A much more effective method of which the writer has had recent first-hand experience, is by spraying the hair thoroughly with a pyrethrum and kerosene mixture. The patient should be given a small towel to hold over her face, the hair is then sprayed thoroughly from all directions with a no. 15 de Vilbiss atomizer, care being taken that the lotion reaches all the roots of the hairs.

The lotion is made with one part of 'pyroicide 20', or any other concentrated pyrethrum extract and 19 parts of white kerosene or deobase oil which is scentless. To this a little (one per cent) of citronella oil may be added to give the lotion a smell, but it is not necessary.

Underclothing removed can be disinfected in 2 hours and gloves, boots and other clothing autoclaved, a comparatively few minutes will kill lice and boots and other clothing for 12 hours to 0.2 per cent of this.



Repeated inspection of the clothing of personnel, especially the menial personnel, of a hospital is an essential measure to maintain freedom from lice. A lens will facilitate the search for lice and their eggs, special attention should be paid to the seams of the underclothing.

For the delousing of troops or infested populations, a very well-organized delousing station is necessary. This must include an entrance room for undressing, with side rooms for dirty underclothes, the disinfection of outer clothing, and the safe-keeping of money and other valuables, from this room the individual passes through the barber's room, the washing room, and the medical-inspection room to the dressing room where he is issued with clean under-linen, and receives back his outer clothing and valuables.

The introduction of DDT has simplified delousing, a 10 per cent powder in pyrophyllite and 6 per cent spray in benzyl-benzoate being convenient forms. Clothes can be rendered louse-proof for several weeks by impregnation with a 2 per cent emulsion.

### TREATMENT

The general and dietetic treatment will be that of any short febrile disease. It is not necessary to force food during the febrile period, but a fluid diet of about 1,000 calories with plenty of additional fluid will be sufficient. The calorie intake may be doubled during the intermission, but the patient should not be given the free run of his teeth during this period as he may be ravenously hungry. The diet at this time should be well balanced and still mainly fluid.

Rest in bed is important, it will be observed naturally during the febrile attacks, but the patient should be warned seriously of the danger of collapse and heart failure during the early intermission period.

Mouth sanitation should be given special attention.

**Specific treatment**—The arsphenamine preparations have a rapid specific action. Novarsenobillon has proved the best drug in the writer's experience, but any of the well-known preparations can be used. A single dose of 0.6 gramme for a normal male adult, and a smaller dose in others on the basis of about 0.01 gramme per kilogramme body-weight should be given, a second dose is seldom necessary and should only be given if a relapse occurs.

... .. for three or four days of the  
will be as well  
even just before  
relapses follows  
if the cases no  
relapse occurs it may be possible to dispense with the specific treatment altogether. This may be important in an epidemic when cost and/or the supply of drugs have to be considered, arsphenamine can in such circumstances be reserved for severe cases only.

... .. for action on this infection in animals (Augustine  
(21 million units) is too large

### PROGNOSIS

After one adequate dose of arsphenamine the relapse incidence will not exceed 15 per cent.

The death rate varies very considerably from epidemic to epidemic, and according to the circumstances. Figures from 1 to 50 per cent are quoted, but the latter high figure would only occur in a starved or exhausted population.

### TICK-BORNE RELAPSING FEVER

fever in Africa was conveyed by the spirochæte in African ticks. This definitely showed that infection

Later other workers discovered other transmitters of the disease in other countries (see p. 224).

### EPIDEMIOLOGY

**Geographical distribution**—This form of the disease has a typically

Brazil and Argentina in Mexico and a number of western and mid-west states of the U.S.A., California, Colorado, Arizona, Texas, and Kansas.

**Epidemic features**—It is essentially an endemic disease and it occurs sporadically in the countries mentioned above. Children are very likely to be infected whilst playing on the ground, as thereby they come into closer contact with the ticks. It is a regional or even a house infection, a history of a succession of infections amongst visitors to a house has often been obtained.

Temperature is an important factor controlling the development of the spirochæte in the tick. In tropical countries, the disease is perennial, but in the sub-tropics, cases occur mainly in the spring and summer, when the ticks are always most active.

### ÆTIOLOGY

The causal organism, as has been stated above, is morphologically identical with *Spirochæta recurrentis*.

**Transmission**—It is believed by some workers that *S. duttoni* was originally a parasite of *Ornithodoros moubata* and that man was only infected incidentally, there is evidence that once infected, *O. moubata* is capable of maintaining the infection through many generations, if not indefinitely, and transmitting it to man so that the cycle of infection is as shown in figure 56. However, clean ticks may become infected through feeding on an infected man. The spirochætes are taken into the insect's gut with the blood meal, after disappearing for a few days, they reappear and invade practically all the tissues of the insect host. They are found in large numbers in the body cavity fluid, where they multiply. The

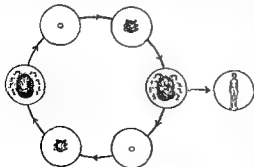


FIGURE 56 The transmission cycle in African (*moubata*) tick-borne relapsing fever.

spirochaetes enter the body cells, including the cells of the ovaries, and are transmitted to the next generation through the ovum

In the case of the other vector ticks, *Ornithodoros erraticus*, for example, the infection dies out after passing through two or three generations, and

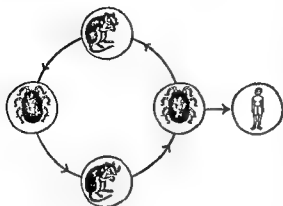


Figure 57 The transmission cycle in other tick-borne (e.g. *erraticus*) relapsing fevers

the tick only becomes reinfected after feeding on an infected mammal. Unlike *O. moubata*, that feeds on man only, these other ticks feed on their natural hosts, rodents and small carnivores, which act as reservoirs of infection, and they transmit the infection to man sporadically (see figure 57)

The actual method of transmission is a matter of controversy, but, as diverse results have been obtained by reliable workers using different vectors it is more

mission will take place by each one of some ticks transmission will be by more three, Buxton (1939) believes that in *O. moubata* the coxal fluid is the only medium of infection. It seems very unlikely that, in nature, transmission would take place by the tick being crushed on the skin, ticks are far too tough for this, though experimentally it is possible to cause infection in this way.

They feed normally on mammals, foxes have been found to transmit the disease by picking

### PATHOLOGY

The pathological lesions are very much the same as in louse-borne relapsing fever, but this spirochæte shows a greater tendency to attack nerve tissue. In experimental infections in mice the spirochætes can always be recovered from the brain, the clinical evidence of this neurotropism is the frequency with which neuritis and paralysis occur as a sequel.

The blood picture is the same as in the louse-borne infection, the spirochætes are usually scantier, and the thick drop method may have to be adopted to find them. A positive Wassermann reaction appears to occur in this disease in 10 to 20 per cent of cases, irrespective of syphilitic infection.

### SYMPTOMATOLOGY

In each different relapsing-fever area, the disease shows a somewhat different picture, only the special features of the various types, as they

differ from the louse-borne infection, as well as from one another, will be indicated

The special features of the African type are —

The incubation period tends to be slightly longer, seven to ten days, the febrile period may be much shorter, lasting only a day or so, but in some

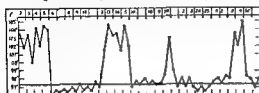


Figure 58 Temperature chart in tick borne relapsing fever (original)

(‘afebrile’ period) seldom remains quite normal but is irregular, frequently rising to 99.5°F or 100°F. Occasionally, the fever loses all its relapsing character and becomes intermittent.

The relapses are far more numerous as many as eleven have been reported.

In some outbreaks, fulminating cases occur in which there is severe jaundice, hæmorrhages, and coma, and the patient dies within 48 hours.

The common complications are bronchitis and pneumonia, as in the other forms of relapsing fever, but in tick relapsing fever, the special sequelæ are diarrhœa and dysentery, neuritis, spastic paralyses, aphasia, strabismus, deafness, hemiplegia, and fortunately very rarely, atrophy of the optic nerve. Parotitis and iritis also occur. The cerebrospinal fluid may be under increased pressure in it, spirochætes are sometimes found, and there is usually an increase of lymphocytes.

In the Iranian type the disease is milder, the initial pyrexial bout usually lasts four or five days, there may be deep remissions, and there are a number, usually four or five, relapses of much shorter duration, not usually more than three days. The attack is usually relatively mild, but severe attacks have been reported.

The Spanish type is also mild, but the patient is very drowsy, and prostration may be considerable when the temperature falls. Herpes labialis is common. The spleen and cervical lymphatic glands are enlarged.

There are not usually more than four relapses.

The leucocytosis occasionally amounts to 25,000 per c mm.

#### DIAGNOSIS

The clinical diagnosis will be more difficult than in louse-borne relapsing fever, and the fever will often simulate malaria. The spirochætes also may be more difficult to find in the blood film and thick films should be examined (see p 87), but animals are more easily infected with *Spirocheta duttoni* than with *Spirocheta recurrentis*; in mice the brain should be examined for spirochætes.

#### PREVENTION

The preventive measures to be adopted against this disease must obviously be very different from those employed against the louse-borne infection, however, the possibility that the spirochæte may change its habitat and become adapted to living in the louse should not be forgotten,

and lousiness should be looked upon as a factor in the area of tick-borne relapsing fever against *Ornithodoros moubata*, because floors of native huts and even European houses (old heavily infected huts or houses should be demolished preferably by burning, and replaced by buildings with concrete floors and well-built brick walls. Other houses it may be possible to repair and to make tick proof.

The sites of camps must be carefully selected, and old camp sites and areas near villages avoided.

Sleeping on the floor should be discouraged but old locally-made beds should be avoided.

In the case of other tick vectors preventive measures will be difficult since they live in the caves and burrows of their alternative hosts and only come into man's habitations fortuitously. The control of domestic animals that may bring them in will be an important preventive measure.

For personal protection suitable clothing that will protect from ticks should be worn in 'tick country'. After walking in bush or jungle the legs should be examined any adhering ticks removed carefully and the area from where they have been removed washed with a strong antiseptic. The starved tick does not transmit infection for some hours. The tick must not be pulled off, but touched with a hot cigarette end or some strong insecticide to make it loosen its grip.

### TREATMENT

This is not materially different from that of the louse borne relapsing type (qv). However, since in most of the tick borne types, relapses are far more numerous specific treatment will be indicated whenever it is available. The infection is more resistant to treatment, and the injections will often have to be repeated.

### PROGNOSIS

The average death rate is about 6 per cent. Some types are very mild but from time to time a fulminating outbreak of the African type occurs with a death rate of at least 50 per cent.

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## RAT-BITE FEVER

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**Definition** — Rat bite fever is a fever of relapsing type caused by micro organisms that are conveyed to man by the bite of small animals mainly rats

**Discussion** — All recent evidence suggests that the parasite principally responsible for this disease is the spirochætal micro organism *Spirillum*

*minus* — However, the careful work of Schottmüller (1914) and others who inoculated with the blood of rats cannot be ignored, and recent work may be the commoner cause.

and Das Gupta (1928) in every other case they found the latter organism, and from this they concluded that, in India at least, *Spirillum minus* is the sole causal organism and that the presence of a streptobacillus was an accidental association. The disease caused by *Spirillum minus* will be described here.

**Historical**—The disease has been recognized, in Japan and elsewhere, as a clinical entity for many years, in Japan it was known as *sodoku* (so=rat, doku=potion). In India, the first clinical record was in 1913. However, the discovery in 1916 by Futaki and others, of the causal organism gave the disease a more concrete form.

### EPIDEMIOLOGY

**Geographical distribution**—This is probably world-wide, but the tropical association of the disease is not solely a matter of poor sanitary and social conditions, though these undoubtedly play an important part, climate *per se* is probably a factor. Most of the earliest cases were reported from Japan. Knowles and Das Gupta (1928) drew attention to the fact that it was a common disease in India and certainly in Calcutta, and the subsequent annual reports of the School of Tropical Medicine have borne this out, between 50 and 100 cases are seen annually at the out-patient department of the School.

Isolated cases have been reported from many countries. The first definite report of a case in the United States was made by Shattuck and Theiler in 1924, and Bayne-Jones (1931) collected 75 apparently authentic cases from the literature, *Spirillum minus* had been isolated in only five of these cases.

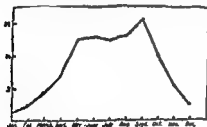


Figure 59 Seasonal incidence of 455 cases of rat-bite fever in Calcutta between 1931 and 1936

(Chopra Basu and Sen 1939)

**Epidemic features**—It is essentially a sporadic disease, it occurs in those living under insanitary conditions and most subject to the bites of rats, the published records of age and sex incidence reflect only the age distribution of the population from which they are drawn, but there is a definite seasonal incidence.

year (see figure 59)

### ÆTIOLOGY

**Historical**—The causal organism was first reported upon by Vandyke Carter in 1887 in India. He found it in the blood of rats but did not associate it with the disease. Others reported a similar organism found in other rodents but Futaki *et al* (1916) were the first to associate it with the disease and isolate it from an infected patient. They named it *Sprocheta morsus muris*. The organism differs from the true spirochetes in possessing flagella, and its correct name is *Spirillum minus*. [The streptobacillus isolated by Schottmüller (1914) and later by others (*vide supra*) cannot, in the opinion of Topley and Wilson (1938), be ignored as the possible cause of a similar form of fever but the *Spirillum minus* infection undoubtedly has a more tropical distribution.]

The causal org -  
measuring from 2



Figure 60  
*Spirillum minus*

dark ground illumination, the rapid, darting, and progressive movements of the organism can be studied, these movements are effected by means of terminal flagella—of which there are several at each pole—and are very different from the backward-and forward movements of the spirochaetes. Multiplication takes place by transverse division.

The spirillum stains well with Giemsa's or other Romanowsky stains, but for demonstrating the flagella Tribondeau's modification of Fontana's silver impregnation method is perhaps the best. The spirilla can be shown in the tissues by this method.

Cultivation of the organisms has been claimed by Futaki and others, but it is not at present a practical procedure.

The infection is readily transmissible to laboratory animals—monkeys, guinea-pigs, rats and mice, the last-named are most commonly used. It has been claimed that the infection is transmitted from the mother to the young, either by intra uterine or by milk infection. Das Gupta (1938) however failed to confirm this observation, as also to infect mice by feeding them on contaminated food. Nevertheless it is not uncommon for one's whole stock of laboratory mice to become infected naturally.

**Distribution in the tissues**—In man the spirillum is found in the local tissues at the site of the bite, in the lymphatics draining the area, in the lymph nodes on the course of these, and in the blood. It has also been demonstrated in the liver, spleen, kidney and suprarenals.

In animals, it appears in the blood in about six days, and it has a predilection for the connective tissues of the nose, the lips, and the gums. Infection of the conjunctival sac is apparently common, the organisms being found in the secretions. The salivary glands are not infected.

**Transmission**—This is effected by the bite of an infected rat or other small animal. The tissues around the mouth are particularly

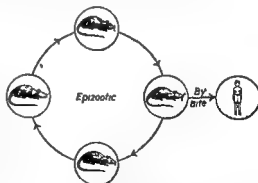


Figure 61 The transmission cycle in rat bite fever

usually it usually damages its gums, contaminates the wound. Another is infected by the conjunctival

**Animal reservoirs of infection**—Wild rats constitute the main reservoir, 3 per cent of wild rats in Japan have been shown to be infected. In



Calcutta, infected rats have frequently been found. After the rat, the cat is the most common agent of infection, and instances have been reported of a similar disease following the bites of weasels, ferrets, squirrels (Das Gupta, 1942), and even dogs, it will be noted that most of these are carnivores that habitually kill rats and are likely to have been infected by rats when they were killing them. As infection is apparently not transmissible by the oral route, it is uncertain how it is transmitted from rat to rat.

### PATHOLOGY

Locally, there is hyperæmia and œdema of the skin and subcutaneous tissues, with polymorphonuclear and eosinophil infiltration. Similar changes will be found in the lymph nodes that drain the area.

and  
epith  
the centre of the liver lobules, have been described

Hyperæmia  
the tubular  
yma cells in

In the rat, there appears to be little tissue reaction to the infection. The liver may show some congestion. In mice, there may be conjunctivitis and loss of hair. Young guinea-pigs usually show emaciation, keratosis, and other eye complications, and die within two months.

**Blood picture**—There is an increasing anæmia if the disease is allowed to progress untreated, but this is not very evident in cases in which treatment is instituted early. With the onset of fever, there is a sharp rise in the leucocyte count, which subsides during the remission periods; there is a relative increase in eosinophils and a decrease in lymphocytes.

**Urine**—A cloud of albumin is common and, more rarely, granular casts appear.

The Wassermann reaction is reported to be positive in this disease. Our experience in Calcutta contradicts this. Das Gupta chose Wassermann reactions experimentally with *Spirillum*. Wassermann reactions become Kahn reaction is frequently negative, the writer has

### SYMPTOMATOLOGY

A definite history of a rat bite may be given, but, as the majority of bites occur at night, much more frequently the patient says that he was awakened by a sudden pain in his foot or hand, and that next morning he found an inflamed local lesion which was obviously a bite.

The incubation period is very variable, but the average is about two weeks, instances as short as three days and as long as several months have been reported. The initial lesions made by the bite may heal in a few days, this will depend on the degree of sepsis. Then, after the incubation period, the true onset will occur suddenly with a high rise of temperature and often a rigor, headache, pains in the joints and muscles, and a considerable degree of prostration. With the first and sometimes with each subsequent febrile paroxysm, there is a local response of the allergic type with redness, swelling and œdema at the site of the original lesion, and, if this has not healed, there will be an increase in the amount

of discharge. The reaction may also occur in the proximal lymph nodes, which were possibly swollen previously but had meanwhile subsided.

At the same time a rash may appear on different parts of the body,

relapses

The rash is by no means common, it occurs in less than 2 per cent of our Calcutta cases.

The fever rises sharply to 103° or 104°F and may remain as a high remittent temperature for three or four days, it then falls to normal within a

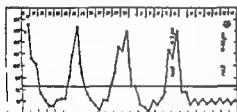


Figure 62 'Rat-bite fever' after a bite by a squirrel (Das Gupta 1942)

A classical temperature chart of rat bite fever showing regular periodicity and response to arsphenamide

few hours, where it remains for a variable period but not usually more than a week (see figure 62). The second rise of temperature is usually as high as the first but the duration is shorter, if no specific treatment is given these relapses may occur at intervals of from 6 to 10 days for many months, but, as a rule the febrile paroxysms become less and less in height and duration, and eventually the infection disappears spontaneously.

The rhythm of the paroxysms may be disturbed by sepsis, and the temperature may show a moderately high, irregular curve in which the paroxysms are scarcely distinguishable (see figure 63).

### DIAGNOSIS

A clinical diagnosis can often be made on the history alone, definite or circumstantial evidence of a rat bite which healed in a few days, an interval of about a fortnight, and a sudden attack of fever with a focal reaction, even before the relapsing nature of the fever with its characteristic periodicity (longer than malaria and shorter than relapsing fever) becomes apparent, are sufficient to establish a diagnosis with a considerable degree of certainty.

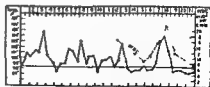


Figure 63 Temperature chart and leucocyte count in rat-bite fever

There are three practical laboratory methods of confirming the diagnosis: (a) by direct examination of serous exudate taken from the initial lesion, (b) by the immobilization test with the patient's serum and (c) by animal inoculation with exudate or blood.

(a) Examination of local lesion.—The hyperæmic or œdematous area around the site of the bite is pricked with a sterile needle, after sterilization

of the area and subsequent washing with normal saline, and the exudate

characteristic shape, as well as by its movements, now slowed down.

Films made from the exudate stained by Leishman's or Giemsa's stains will often show the spirilla quite well, but Tribondeau's modification of Fontana's stain gives the best results, the technique of this method is described by Das Gupta (1938) as follows —

(i) A thin film of the clear serous exudate is prepared from the lesion on a clean slide and allowed to dry in the air

(ii) The slide is fixed with Ruge's solution, which has the following composition: 1 ccm solution of formaldehyde 2 ccm fixative is poured on and drained off, this about a minute

(iii) The fixative is drained off the slide which is next covered with methyl alcohol and flamed by applying a lighted match. This completes fixation

(iv) The slide is laid on the staining rack and flooded with the following mordant: tannic acid 5 grammes, in distilled water, 100 ccm. It is gently warmed until steam rises. The best and least messy way of doing this is to wrap a little cotton-wool round the end of a piece of wire, soak it in alcohol, light it and hold under the slide. When steam rises from the slide the flame is removed and the mordant allowed to act for thirty seconds longer without further heating

(v) The slide is washed with distilled water and then covered with Fontana's silver solution. To prepare this a 5 per cent aqueous solution of silver nitrate is taken in a glass cylinder which has previously been thoroughly washed with distilled water. With a capillary pipette a strong solution of ammonia is added drop by drop. A sepia precipitate forms and then re-dissolves. To the now clear solution a few drops of formalin are added very carefully, and only drop by drop, which is just opalescent. The slide is covered with the silver solution and the flame is removed after thirty seconds.

(vi) The film is washed in distilled water and allowed to dry in the air. It should never be blotted.

The film is then examined with an oil immersion lens. The spirilla are stained an intense brown black or black against a faint yellow background.

The spirilla are usually scanty and a determined search for them has to be made. They were found in 64 per cent of our Calcutta cases believed on clinical grounds to be cases of rat-bite fever.

(b) Immobilization of spirilla with patient's serum — Blood is taken from an infected mouse's tail and mixed with a 1-in-5 dilution of the patient's serum in normal saline. A coverslip is applied and the specimen sealed with vaseline. Examined after an hour, the spirilla will be immobile if the patient is suffering from rat-bite fever, but still very active in the blood of a patient with a positive result. This method helps to exclude other causes.

(c) Animal inoculation — The most suitable animals are — (i) *White mice* the limitation is that these animals are very subject to 'natural' infection, so that clean stock has to be used and the mice examined thoroughly before inoculation. (ii) *Young guinea-pigs* in these the development of the infection is slower and perhaps less certain. (iii) *Other animals* these include adult guinea-pigs, rabbits and monkeys.

The inoculation is made either from the serous exudate from the lesions, a drop of which is given subcutaneously, or from the blood, 0.5 c.c. being given intraperitoneally to a mouse, 1 c.c. to a young guinea-pig, and 2 c.c. or more to any of the larger animals used.

Spirilla were identified in 70 per cent of our clinically typical Calcutta cases by blood inoculation into white mice.

**Therapeutic test**—One adequate dose of arsphenamine will always interrupt, at any rate temporarily, the periodicity of the fever.

**Differential diagnosis**—The conditions likely to be confused with rat-bite fever are—

(i) Septic fever from the bite this will usually follow the bite almost immediately.

(ii) Filarial lymphangitis and fever microfilariae will usually be found in the blood taken at night.

(iii) Relapsing fever the 'disease period' is usually much longer, and spirochaetes will be found in the blood.

(iv) Malaria the periodicity is much shorter malaria parasites will be found in the blood and the fever will respond to anti-malarial drugs.

Rat-bite fever may simulate other short febrile diseases, such as dengue sand-fly fever, and influenza, but the diagnosis will be cleared up when the characteristic periodicity of the fever becomes apparent.

### TREATMENT

The prophylactic treatment of a rat bite consists in applying pure phenol to the wound with a match stick swab, washing this out with sterile water, putting powdered sulphanilamide into the wound, and applying a dressing.

Specific treatment is provided by any of the arsphenamine group of drugs given according to the weight of the patient (see p. 232). Usually two injections will effect a complete cure, but it may be advisable to give a third.

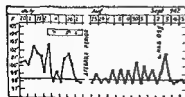


Figure 64 Sulphapyridine appeared to effect a cure but *Spirillum minus* was still present in the blood and the fever relapsed.

Sulphapyridine given in the usual doses appears to control the fever temporarily in some cases, but it does not effect a cure. In the case of which the temperature chart is shown in figure 64 spirilla were found in the blood until novarsenobillon was given.

### PROGNOSIS

If adequate treatment is given, complete recovery may be expected by the time the local lesion settles down and the death rate in our experience has been negligible. In Japan, however, a death rate of 10 per cent has been reported.

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Addendum.—Penicillin has proved most effective in the treatment of an infection with either *Spirillum minus* or *Streptobacillus moniliformis* (Heilman and Tully, 1944, Proc Staff Meet Mayo Clin, 19, 257)

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## SEVEN DAY FEVER OF JAPAN

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other similar but distinguishable syndromes which are as yet not clearly differentiated

The name 'leptospirosis' are grouped have many common clinical and caused by organisms of the genus *Weil's disease* or infective jaundice, but there are probably many

*Leptospira* is the generic name of a group of spirochæte-like organisms, they have tightly-wound spirals, which give them the appearance of a twisted rope, and, usually, hooked ends. They live saprophytically as well as parasitically. The commonest species is *Leptospira biflexa*, which is found in water supplies in many parts of the world and is a filter-passer. The parasitic species infect rodents and man causing in the latter diseases of the group under discussion.



Figure 65  
*Leptospira*

### WEIL'S DISEASE OR INFECTIVE JAUNDICE

**Definition**—Weil's disease is an acute infectious disease of sudden onset, characterized by fever, jaundice, albuminuria, hæmorrhages from mucous surfaces, extreme prostration, muscular pain and tenderness and occasionally a petechial rash, it is caused by a spirochætal organism of the genus *Leptospira*, which is a common infection of the urinary tract of rodents and which infects man through abrasions in the skin and mucous membranes, or by the oral route.

**Historical**—Infective jaundice is not a new disease. Early in the nineteenth century French writers described the disease and reported small outbreaks of it in Europe. In 1886 Weil gave a clear description of the disease and from that history, ly more ver in tospirai Weil's disease and it was soon shown to have a widespread distribution.

### EPIDEMIOLOGY

**Geographical distribution**—It occurs in Japan, Holland, Great Britain, France, Germany, Sweden, and other tropical countries. In Japan, about 100 cases, in European countries a varying number, probably more or less in proportion to the amount of attention that is paid to the disease. During the 1914-18 war, the disease was common among the troops serving on the Western front. So far as India and her immediate neighbours are concerned, a small number of cases have been reported from time to time by different workers from several places such as the Andamans (Barker, 1926), Rangoon, Calcutta, Bombay, Madras, and the North-West Frontier Province. In most of these places the disease occurs in a sporadic form. For example, in Calcutta within the last seven years some 50 or more cases have been reported. In the Andamans, a sharp outbreak occurred in 1929 in which less than a hundred cases were recorded, but now that its presence has been recognized a large number of cases have been diagnosed each year.

**Epidemic status**—On account of the very low incidence, the disease is not at present one of very great public health importance in any tropical

country with the possible exception of the Andaman Islands but there are indications that it may be much more widespread than it appears to be at present

In temperate countries its occupational character stands out so clearly that it comes within the purview of workmen's compensation acts. It occurs in those who come in contact with water or slime contaminated with the urine of infected rats. Sewer and canal workers, miners, fish handlers and butchers, agricultural labourers, sugar-cane cutters, bargemen and soldiers fighting in trenches are liable to suffer from it.

In the Andamans the disease is found chiefly amongst agricultural labourers many of whom are adult males who have to work standing in water during part of the year. However in Calcutta Das Gupta who has confirmed the diagnosis in 40 to 50 cases during the last few years found no association with any particular occupation. Moist soil, moderate temperature, insanitary conditions and rat infestation favour incidence. In cities sporadic cases may occur amongst the general population. The larger outbreaks are generally confined to swampy areas, to mines and to canal and coastal regions but even in the largest outbreak the number of cases is never more than a few hundred.

**Seasonal incidence**—In cooler countries it is a summer and autumn infection but in the tropics the disease occurs most frequently during or after the rains and with the onset of dry cold weather it tends to disappear.

**Race, sex and age incidence**—It occurs in people of all races and in both sexes but few cases have been reported amongst children. The majority of the occupational groups have consisted of men only but in the case of the fish handlers they were mostly women.

## ETIOLOGY

**The causal organism**—*Leptospira icterohæmorrhagica* is a spiral organism 6 to 9  $\mu$  long and 0.25  $\mu$  thick. It has a large number of 1-1 wound spirals which give it a hooked appearance. It is actively motile. It grows on illumination. It grows on Vervoot's medium but takes a week to grow.

**Serological strains**—There are a large number of serological strains of leptospira known. Of these at least three strains have been recovered from the cases occurring in India. Whilst there is a tendency towards a geographical grouping of these strains in the same outbreak more than one strain may be isolated. The canicola strain is common in the United States.

**Resistance**—*Leptospira icterohæmorrhagica* is a comparatively hardy organism and can survive in water at 100° F. for 10 days.

in ten minutes

a blood infection during period leptospira will be in liver, spleen and kidney and the kidney becomes





balance of evidence is, however, in favour of the rat's playing some essential part in the transmission of the disease to man

**Route of entry**—The organisms enter either by the mouth or through the skin. The latter is considered to be the more frequent route of entry. Organisms generally enter through abrasions in the skin, though they are capable of penetrating even the unbroken skin and mucous membrane. Prolonged contact with infected water and soil facilitates entry. Bathing and accidental immersion in infected water have frequently given rise to the disease, and in Holland it is the commonest mode of infection.

**Immunity**—From the sporadic nature of the incidence of the disease, even in the presence of a heavy source of infection, it would appear that man enjoys some natural immunity against leptospira infection. After recovery from an attack of the disease, a high degree of immunity develops. This acquired immunity is mainly due to the presence of specific antibodies. Convalescent serum has therefore been used in treatment (*vide infra*), as well as the serum of immunized horses, which in some countries has been used extensively. Active immunity can be produced in man by means of a specific vaccine. Das Gupta (1942) found that after inoculation, antibodies protective to guinea pigs appeared in the blood but disappeared within a year.

### PATHOLOGY

After an initial leptospiraemia, toxins produced by the leptospira damage

**Morbid anatomy.**—The liver is enlarged and usually yellow, there is degeneration of the parenchyma cells which will vary from degeneration of isolated cells, to similar changes in localized areas, and to complete disorganization of the whole liver structure, similar to, but usually not so extensive as, the changes that occur in yellow fever. Where isolated parenchyma cells are affected, they die, but are replaced, so that, unless the damage is very extensive, complete recovery is possible.

In the kidneys, there is invasion of the inter-tubular tissues where small hæmorrhages occur, and degenerative changes occur in the tubular epithelium, regeneration follows in the latter case, but the interstitial changes will sometimes, though rarely, lead to a chronic nephritis.

The spleen is slightly enlarged but is soft and diffuent, so that attention is not usually drawn to it clinically, there is hyperplasia of the lymphatic tissue.

Similarly, there is hyperplasia of the lymph nodes in other parts of the body, particularly of the abdominal glands. The bone marrow shows leucoblastic hyperplasia with erythroblastic depression. There may be cellular infiltration of the stomach and intestines, and leptospira are

**Blood picture**—There is usually a leucocytosis of 10 000 per mm, a polymorphonuclear percentage of 80 to 85 with a leftward shift in the Arneeth count, and a progressive anaemia, the indirect van den Bergh reaction

is usually positive even in an-icteric cases and in the cases with jaundice it is biphasic and may reach 60 units of bilirubin

**Urine**—There is usually a heavy cloud of albumin and often traces of blood, occasionally, hæmaturia may reach macroscopic proportions. There is sometimes a decrease in the urea excretion, and later, after a period of anuria, there will often be a temporary increase. Later, in the jaundiced cases, bile will appear

### SYMPTOMATOLOGY

The attacks vary very considerably in intensity and from serological

The three pathological phases of the disease the leptospiræmic, the hepatic and the renal may not be clearly defined clinically. Liver damage becomes evident from the fourth or fifth day and the renal only in the severest cases about the tenth day

The incubation period is from four to twelve days and the onset is usually sudden. The fever mounts rapidly to reach  $102^{\circ}\text{F}$  or  $103^{\circ}\text{F}$  on the fourth day, continuing as a high remittent fever for a few days and then falling by lysis, the whole attack lasting about 10 days. A febrile relapse after about three or four days of freedom from fever is not uncommon. In severe and complicated cases the fever may last much longer, and tends to occur in a series of relapses

The pulse is rapid at first but often slows

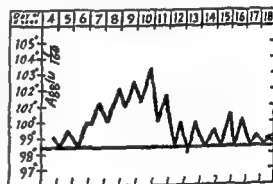


Figure 67 Temperature chart in Weil's disease

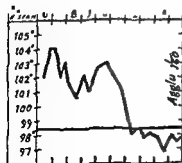


Figure 68 Case showing an early fall of temperature

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at least one coat with

hæmorrhages from other mucous surfaces may occur. Rashes are not constant, a petechial rash may appear from the third to the fifth day, and a morbilliform rash from the fifth to the twelfth day. In very severe cases the rash is hæmorrhagic

**Anuria** is not uncommon, and, even when some urine is being excreted, there is evidence of nitrogen retention

The hair tends to fall out, and, in milder forms of this infection, this is sometimes the first observation of the patient

The liver is usually palpable and the spleen occasionally so, the former is nearly always tender

**Complications**—The most important complications are bronchitis and broncho pneumonia, this is particularly true in cold countries

Iritis and irido-cyclitis have been described in some countries

**Relapses**—In about 30 per cent of febrile cases, there is a relapse of the fever at the end of the third, or early in the fourth, week. This recurrence of fever is not accompanied by any reappearance of the leptospiræ in the blood, and is therefore not a true relapse comparable with that which occurs in certain other spirochætal diseases. In this second bout, the fever does not usually rise much above 100°F, the temperature is usually irregular for a few days, and then falls again to normal

## DIAGNOSIS

The diagnosis of Weil's disease, with any degree of certainty, on clinical grounds alone, is not easy, especially in cases in which there is no jaundice. Demonstration of the causal organism in the blood or urine is the surest method of confirming the diagnosis but strong presumptive evidence may be obtained from the agglutination test

Leptospiræ are present in the blood of patients during the first week of illness, and can be isolated readily even as late as the ninth day. Microscopic examination of the blood either by means of stained films or by dark-ground illumination is of little practical use as the leptospiræ are scanty and therefore very difficult to find by this means

Cultural examination gives fairly satisfactory results. Vervoot's medium is the best to use, into 10 ccm of Vervoot's medium 1 ccm of blood is inoculated and the medium is incubated for at least one week either at room temperature or at 28° to 30°C. In 60 to 100 per cent of cases examined within the first week, positive results are obtained

Animal inoculation is perhaps the most reliable method of diagnosis. Three to five cubic centimetres of blood are injected intra-peritoneally into young guinea-pigs weighing about 250 grammes and their peritoneal fluid examined for leptospiræ by dark ground illumination from the seventh day onwards. If the animal dies, a post-mortem examination is done, and sections of the liver and kidney are stained by Levaditi's method and examined for leptospiræ

The urine of patients may also show leptospiræ, they appear in the urine from about the tenth day of the illness, and may continue to be excreted for two months. Repeated examinations are however necessary

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Serological methods for the diagnosis of Weil's disease have also been developed. The patient's serum and a weak formalinized culture of

leptospiræ are used, agglutinins begin to appear in the blood about the sixth day of illness, and are present for years after recovery. Positive results in dilutions as high as 1 in 10,000 are common, and occasionally the titre rises to 1 in 1,000,000, but an agglutination of 1 in 100 is considered specific by some workers. Such a low titre might indicate past infection, and, in the Widal test, more attention should be paid to a rising titre. As there are several serological strains of leptospiræ, the serum should be put up with all the strains that are available. In some cases the urine also gives a positive agglutination test up to 1 in 250 dilution.

Recently, Brown (1939) has described an adhesion test for the diagnosis of Weil's disease. The patient's serum is mixed with a young culture of leptospiræ, a living culture of some motile bacillus, and fresh serum from a guinea-pig, the mixture is incubated at 37°C for half an hour. It is then examined under dark-ground illumination. A positive result is indicated by the motile bacilli adhering to the leptospiræ.

### DIFFERENTIAL DIAGNOSIS

In severe cases, the clinical picture will suggest yellow fever, in less severe cases 'bilious remittent' malarial fever or relapsing fever, in the last two, blood examination will clinch the diagnosis. In cases in which jaundice is prominent, catarrhal jaundice will have to be excluded, but the fever will be lower and the prostration less in the latter case. Severe hæmaturia may simulate the hæmoglobinuria of blackwater fever, but careful investigation will distinguish them. Mild cases may suggest dengue, or sand-fly fever but the leucopenia which is the rule in these conditions, as well as the shorter duration of the fever, should help to distinguish them.

### PREVENTION

Successful control and prevention of Weil's disease depends upon—(a) the destruction of rats, (b) the disinfection of infected water and soil, (c) the protection of persons who are exposed to infection, and, in some circumstances (d) the diagnosis and treatment of cases and disinfection of their urine.

(a) *The destruction of rats*—As rats are the main source of infection, war against rats is of the greatest importance. Food stores and supplies should be protected by rat-proofing. Attempts should be made to trap or poison rats and reduce their numbers.

(b) *The disinfection of infected water and soil*—Contaminated water should not be used for bathing, washing, or drinking. Infected water and soil should be disinfected, the latter by the use of calcium cyanamide, this is a fertilizer and is of special value in damp and water-logged agricultural areas. About 168 lb of calcium cyanamide are required for one acre of soil. For the disinfection of water in paddy fields, 44 lb of the fertilizer should be used per acre for each inch of depth of water. Leptospiræ generally thrive in alkaline soils. Acidifying the soil also helps to destroy the organisms. Wherever possible, drainage of the soil should be effected.

(c) *The protection of persons who are exposed to infection*—People

clean soap and water. Persons with achlorhydria should be particularly

careful Cuts and abrasions received by workers should be promptly disinfected

In population groups under special risk vaccination should be considered but as there are a number of serological strains of leptospira, the choice of the vaccine, in order to be effective should consist of 50 to 75 millions of organisms should be given at an interval as the vaccine has helped considerably in Japan The protection is however apparently short lived and re-vaccination should be carried out at regular intervals of certainly not less than a year

(d) *The diagnosis and treatment of cases and disinfection of their urine*—Cases should be diagnosed early and admitted into hospital, if possible Their urine should be disinfected Convalescents should be detained until their urine is free from leptospira

Convalescents may be re-employed as labourers about two months after recovery It is advantageous to employ them as they will be immune to infection

### TREATMENT

The only specific treatment that has been effective is specific anti-serum, either horse serum which has now been prepared on a commercial scale or convalescent serum An initial injection of 60 ccm of horse serum in a pint of saline should be given intravenously, with the usual precautions against anaphylactic shock this should be repeated next day, and each day, as long as it is indicated by the patient's condition A polyvalent serum, or better still one prepared from all local strains should be used Of convalescent serum about 30 ccm is usually given and this is also repeated if necessary

Arspenamine has no specific action in this infection

A pint of 5 per cent glucose in pyrogen free water and 5 units of insulin should be given as long as there is evidence of toxæmia In less severe cases isotonic rectal saline with 4 grains of calcium chloride to the pint is useful

Otherwise the treatment is symptomatic and must be indicated by the complications that arise The patient should be confined strictly to bed until some days after the temperature has fallen to normal and he should be kept on a fluid diet glucose albumen water and lime whey at first then milk and the diet should be increased very slowly during convalescence (See note on p 308 regarding high protein diet)

### PROGNOSIS

The mortality from the disease is very variable and ranges from 11 to 50 per cent Death seldom occurs in the anicteric cases but in the writer's experience the death rate even under hospital conditions in cases with well developed jaundice is as high as 50 per cent

Age is an important factor in mild epidemics the deaths are often only amongst persons over 50 years of age The following is the percentage case mortality recorded in different countries in Japan 32 to 48 per cent, in Malaya 30 per cent in India 18 to 40 per cent in Scotland 25 per cent, in Germany 13 per cent in London 4 to 6 per cent in Belgium 4 to 6 per cent and in Italy 11 per cent These figures are based on clinically diagnosed cases and the higher figures probably exclude the mild an-icteric cases

## SEVEN-DAY FEVER OF JAPAN

**Introduction** — This is one of the milder forms of leptospiral infection the syndrome has been recognized in Japan for many years, and is known by the names *nanukayami* or *sakusku* fever. Autumn fever is probably a variant of the same infection. It was distinguished from dengue and shown to be caused by a leptospira (*Leptospira hebdomadis*) by Ido, Ito and Wani in 1918.

There are many recognized strains of *L. icterohæmorrhagica* which differ from one another antigenically but are apparently similar in their pathogenicity, at least, up to the present little correlation between particular strains and degrees of pathogenicity has been demonstrated. The obviously low pathogenicity of *L. hebdomadis* constitutes a difference which at present seems to warrant special differentiation, but nevertheless in time, intermediate strains may be encountered, and it may then be necessary to consider *L. hebdomadis* as simply one strain of *L. icterohæmorrhagica*, in such circumstances, seven day fever will have to be looked upon as a mild form of Weil's disease, which from a clinical standpoint it might well be.

Autumn fever, pseudo dengue, and certain other short fevers of Java and Sumatra will also probably fall into line.

**Epidemiology** — It is a sporadic infection common in certain rural districts of Japan mainly affecting field workers.

## ÆTIOLOGY

The causal organism, *Leptospira hebdomadis*, is morphologically identical with *L. icterohæmorrhagica* but antigenically it is quite distinct. In guinea-pigs, it causes a febrile disease which is sometimes fatal, but it produces jaundice in only about 17 per cent of animals infected, of *L. icterohæmorrhagica* which is almost always fatal and causes severe jaundice in 100 per cent of animals.

**Transmission** — The reservoir of infection is the short eared field mouse *Microtus* in about 3 per cent man by the same.

## SYMPTOMATOLOGY

The onset of this disease is usually sudden, with high fever, headaches muscular pains loss of appetite, glandular enlargement, and occasionally a morbilliform rash. The fever sometimes runs a dengue-like course, and in fact the disease was and probably still is, confused with dengue. Otherwise, it is like a mild form of Weil's disease.

Little is known of the pathology as the prognosis is uniformly good.

The diagnosis is made in the same way as that of Weil's disease.

The main points of distinction between this disease and dengue are the slow pulse and the leucopenia in the latter, the white cell count in seven-day fever is usually about 10,000 per mm, and the increase is mainly in polymorphonuclears.

The treatment is symptomatic, and the preventive measures that can be adopted are based on the knowledge of the reservoir of infection and common-sense application of this knowledge.

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### THE TYPHUS FEVERS

**Definition**—The typhus fevers are a group of febrile diseases of varying severity caused by micro organisms of the genus *Rickettsia* and transmitted to man mainly if not entirely by the agency of insects

**Introduction**—In view of the fact that all the diseases hitherto recognized clinically as typhus have been shown to be rickettsial in origin and that all diseases that are known to be caused by rickettsiæ have

modify this nomenclature. Since there were 27 different names applied to the necessity for clarification and classification, since he wrote this the number has been added. The classification which has been adopted from the point of view between the epidemic

There are many is not expedient nor would it be possible in the space at his disposal to discuss all these the writer proposes to describe only certain clear cut types that have appeared in countries outside India and then to discuss the disease as we see it in India

**Historical**—Typhus fever was distinguished from typhoid fever only about a century ago both by Stolic (1838) and Gerhard (1837) though there are many earlier historical references to epidemics that were almost certainly typhus. It

was always recognized as a very infectious disease, but the manner in which it spread from man to — — — — —  
 Nicolle and Conseil  
 Meanwhile, Ri  
 to guinea-pigs by th  
 finding of the organi  
 lice in Mexico, but  
 tions of these disea  
 (Wolbach 1919, 1'  
 adequate description  
 to the causal or  
 organisms of the same group, which he called *Dermacentrozetes rickettsii* ■ the  
 cause of Rocky Mountain spotted fever Japanese river fever, or tsutsugamushi  
 disease, which had long been recognized clinically and known to be transmitted  
 by mites was shown to be caused by a rickettsia which Sellards (1923) described  
 and called *R. orientalis*, the mild sporadic form of typhus that Brill (1898)  
 described in New York, the slightly more severe but still mild sporadic form  
 that occurred in Mexico and South-East United States (Maxcy, 1926), and  
 'trench fever' that occurred on both sides of the western front in the last war,  
 were also shown to be rickettsial in origin, in 1925, the endemic typhus fevers  
 of Malaya were linked up with this group of diseases by Fletcher and Lumsden,  
 and the position was clarified by Lewthwaite and his collaborators (Lewthwaite  
 and Savor, 1940) In 1937 Burnet and Freeman showed that Australian 'Q'  
 fever (Derrick, 1937) was caused by a rickettsia

Wilson (1909) reported the isolation from the stools of typhus patients of  
 proteus-like organisms that were agglutinated by the patients sera and later  
 Weil and Felix (1916) separated the special strain of proteus that gave a very  
 high agglutination titre with the serum of patients suffering from epidemic typhus  
 thereby introducing the test now usually known as the Weil-Felix or the Wilson-  
 Weil-Felix test, which appears to be positive in most of the typhus fevers and is  
 a further means of identifying them

In 1917 Megaw drew attention to the existence of endemic typhus in India,  
 and suggested the tick as a transmitter

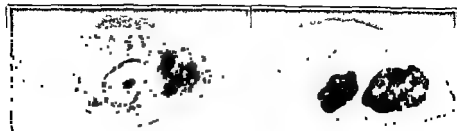
Thus during the last thirty years a number of diseases which occur in  
 many different parts of the world have little in common epidemiologically, and  
 are clinically often very dissimilar have been linked up and shown to be caused  
 by some species of the genus *Rickettsia*. It has only been possible here to  
 outline the story and to mention a very few of the workers involved some of  
 whom including both Ricketts and von Prowazek lost their lives during their  
 investigations as the result of laboratory infections

**Classification**—Since Megaw suggested his classification according to  
 the vector, a considerable advance has been made in our knowledge of the  
 antigenic relations of the various rickettsiae that infect man On an  
 immunological basis, there are four main groups of typhus fever (a)  
 classical typhus (with which endemic typhus is closely related), (b) Rocky  
 Mountain spotted fever (c) tsutsugamushi, and (d) trench fever

The classification that has been adopted here is modelled on Megaw's  
 original classification which has been modified to take into account recent

pod, and enzootic, that is (in this instance) from rodent to rodent. This  
 provisional classification is shown in table IV which also gives some of the  
 outstanding clinical and other features of these diseases

in  
 Sol  
 gro  
 Further reference is made to these below



Pinkerton 1944

## THE RICKETTSIÆ

These are a group of micro-organisms that fall between the bacteria and the filtrable viruses, not or probably in their evolution complete enzyme system that simple che animal or growth any scale and have become obligatory parasites, their enzyme systems have degenerated so far that they are unable to sustain saprophytic existence

The rickettsiæ\* can be divided into several groups according to the distance they have descended in the evolutionary scale

- (i) Non-pathogenic (to mammals) extra-cellular and intra-cellular rickettsiæ, a large number have been isolated from a variety of insects
- (ii) Potentially pathogenic extra-cellular rickettsiæ—e.g. *R. quintana* of trench fever
- (iii) Pathogenic intra-cellular rickettsiæ that will also live extra cellularly under certain conditions, e.g. *R. burnetii* of Q fever
- (iv) Pathogenic rickettsiæ that are obligatory intra-cellular parasites, these are sub-divided into two groups —
  - (a) the intracytoplasmic, e.g. *R. prowazekii* and *R. orientalis* of epidemic typhus and tsutsugamushi respectively
  - (b) the intranuclear, e.g. *R. rickettsii* (*Dermacentorinus rickettsii*) of Rocky Mountain spotted fever, these are also present in the cell cytoplasm

---

\* Rickettsiaceæ (Wolbach, 1940) has been suggested as the family name for this group of organisms, but it would perhaps be more appropriate if a super family Rickettsioidea with families, say, Wolbachiaceæ for the non-pathogenic and potentially extra-cellular organisms and Rickettsiaceæ for the obligatory intra cellular species of the last group, were created

TABLE IV. FEVERS OF THE TYPHUS GROUP

Primary cycle	Epidemic	Enanthropic	Eurotic		
			Sporadic place-diseases communicated from natural reservoirs to man by various arthropods. Mostly diseases of the open country		
			Tick typhus	Flea-typhus	Mite-typhus
		Louse-typhus			
			Rocky Mountain spotted fever, western variety	Eièvre boutou neuve tick bite fever	Toutangamushi Japanese river fever scrub or tropical typhus Sumatra mite fever
Names and synonyms			Rocky Mountain States USA	Europe South America Africa Asia	Oriental tropical and sub-tropical countries
Distribution			<i>Rickettsia</i>	<i>R. conorii</i>	<i>R. orientalis</i>
Virus			<i>Dermacentor andersoni</i>	<i>Rhipicephalus sanguineus</i>	Mites ( <i>Trombicula akamushi</i> and <i>T. deliensis</i> )
Vectors			<i>Dermacentor andersoni</i> (no animal reservoir identified)	Rodents of the fields possibly dogs and other domestic animals.	Rats and mice
Reservoirs of infection			+++ ++ +	+++ ++ +	- to ± - ++ to +++
Serum agglutination res. on to	OX19 OX2 OXK		Maculo-papular common on palms soles and face	As in lower type but often faint or absent	Macular or papular often on face rare on palms and soles
Rash			Nil	Common	Nil
Local sore, lymphangitis and lymphadenitis			Nil	Common	Almost constant in Japanese mite-typhus often absent in other mite-typhuses
Mortality per cent	5 to 50	Very low	High 16 to 50	Low about 10	10 to 20



## CLASSICAL, EPIDEMIC OR LOUSE-BORNE TYPHUS

**Definition**—Classical typhus is a severe febrile epidemic disease with a sudden onset, lasting 10 to 15 days and ending in rapid lysis accompanied by a rash that appears from the third to the fifth day, and caused by *Rickettsia prowazeki* which is carried from man to man by lice

### EPIDEMIOLOGY

**Geographical distribution**—This disease has, or rather has had, a world-wide distribution. It is certainly not 'tropical', though it might be considered *exotique*, it is actually much less common in tropical than in temperate countries.

Recent epidemics have occurred in Russia, Poland, the Balkans, Ireland and Spain in Europe, in North Africa, in Asia Minor, Transcaucasia, Siberia and China, and in Colombia, Ecuador, Peru and Chile.

**Epidemic features**—It is essentially an epidemic disease, and its incidence is clearly explainable on the basis of its mode of transmission. It occurs in the less civilized countries in Europe where the sense of personal cleanliness of the individual is not highly developed, or where through circumstances his normal habits are interfered with, such as during wars, persecutions, and famines. Its absence from many tropical countries can probably be explained by the small amount of clothing worn, which reduces the harbourage of the transmitting louse, and, in the case of India, on the cleanliness of the personal habits of the majority of the population.

In addition to the transmission factor, the lowering of the resistance of the population by hardships and privations is probably important. In such circumstances the natural immunity is reduced, so that the individual not only becomes more susceptible to the disease, but the formation of antibodies is poor and the virus remains in the peripheral blood for a longer period of time under such circumstances, and therefore causes a more severe attack.

Deaths from typhus in England and Wales which numbered about 4,000 annually in 1870 had fallen below 40 at the beginning of the century to disappear from the returns by 1920. The history of the disease in other sanitariously-advanced European countries has been similar.

**Season, race and sex incidence**—In its seasonal distribution typhus is more common in winter than in summer for the obvious reason that people tend to sleep herded together in their huts and wear more clothes in winter.

All races appear to be equally susceptible to the disease but it tends to take a milder form in the races habituated to it (Napier, 1919).

The sexes are equally susceptible, the disease is usually milder in children.

### ÆTIOLOGY

**The virus**—The causal organism is *Rickettsia prowazeki*, the type species of the genus *Rickettsia*. The rickettsiæ are granule-like bodies, more or less pleomorphic, with a diameter of less than half a micron, staining badly with aniline dyes, but well (purplish) with Giemsa's stain, they show a tendency to bi-polar staining. In their behaviour they fall between the filtrable viruses and the bacteria, they do not grow on ordinary



laboratory media, but can be grown in tissue culture medium, or on the yolk sac of the developing chick embryo, which is the method used in preparing vaccines. They are held up by fine filters, while they pass through coarse ones, as do small bacteria.

These rickettsiæ are found in the cytoplasm of the endothelial cells of the blood vessel of their mammalian hosts, in the cells of the gut lining of lice, an intra-cellular position characterizes the pathogenic rickettsiæ and distinguishes them from the non-pathogenic varieties that are also found in certain arthropods. In the blood stream the rickettsiæ tends to adhere to the red cells and platelets.

**Transmission**—The virus circulates in the peripheral blood during the febrile period and desquescence. The louse, *Pediculus humanus*, becomes infected by sucking the blood of its host, which is exclusively man, the rickettsiæ invade the endothelial lining of the gut of the louse, here they multiply, the cells eventually burst into the lumen of the gut, and the rickettsial bodies are passed out with the faeces, the cycle within the louse takes at least three days, usually longer, after which the louse is infective and remains so for the rest of its life. The normal life span of the louse is about 14 days, but survival up to 45 days has been reported, the infection, however, tends to kill them. The rickettsiæ survive in the dried faeces of lice up to 60 days, and the faeces are probably the main source of infection of man and the sole source of infection of the next generation of lice. The extreme infectiousness of typhus depends on the fact that the dried faeces of lice may be blown about in the air of the sick-room or laboratory. Man is infected by scratching the faeces into his skin, by contamination of his mucous membranes, or via the respiratory tract. It is doubtful if gastro-intestinal infection takes place, and it is

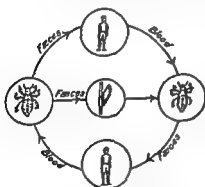


Figure 69. Transmission cycle in epidemic typhus

contamination with the infected faeces of lice, and (c) by air-borne infection from dried faeces of lice. The former two have long been recognized and explain the rapid spreading of the disease when louse infected people are

known that infection is not transmitted by the bite of the louse. The cycle is thus man—louse—man. The louse is an essential link and so probably is man, for *Pediculus humanus* feeds exclusively on human blood, and, though the infection may be transmitted to the next generation of lice by contamination, there is no hereditary transmission and, as the infection is fatal to the louse no louse-to-louse cycle would survive any length of time.

The possible modes of dissemination of infection are by (a) migration of infected lice, (b) by contact of infected lice, and (c) by air-borne infection from dried faeces of lice. The former two have long been recognized and explain the rapid spreading of the disease when louse infected people are

nurses, and during an epidemic of the disease many have died.

**Immunity** —The immunity produced by an attack is not complete, and second and even third attacks have been reported. The comparatively mild form that the disease sometimes takes in communities where it is common can probably be accounted for by the previous attacks that these people have suffered, especially during childhood when the attacks are often very mild and might not be recognized as typhus.

Passive immunity can be conveyed by the injection of the sera of convalescents, but as a practical means of protection this method is of little or no value.

Active immunity can be produced by the inoculation of dead rickettsiae (*vide infra*).

Cross immunity between classical typhus and the so-called Brill's disease has been shown to be complete, this is of course natural. A considerable degree of cross immunity between classical and murine typhus (e.g. tabardillo of Mexico, *vi*) has been demonstrated, though this is not complete, but against the other forms of typhus there is little or no cross immunity. The immunity runs more or less parallel with the Weil-Felix reaction.

### PATHOLOGY

**Morbid anatomy** —There are few macroscopic changes. The spleen is usually distinctly enlarged, on section it is dark red, soft and diffuent. There is cloudy swelling of the liver and kidneys. Waxy degeneration of the muscles has been noted. There are petechial hæmorrhages in the serous and mucous membranes and in the pons and medulla, and occasionally more extensive hæmorrhages into the hollow viscera, the serous cavities, and even into the ventricles.

endothelial  
rickettsiae,  
vascular  
of poly-  
morphonuclears. The tubercular nodules that are thus produced in the organs and tissues are suggestive of miliary tuberculosis. These changes take place in the skin and cause the characteristic rash, in the mucous and serous membranes and cause hæmorrhages in the various organs, and in the central nervous system, the neuroglia cells taking part in the reaction, and cause the mental symptoms.

There are no very characteristic changes in the blood picture. In severe cases, especially when the patients first come under observation and are suffering some dehydration, there will be polycythæmia, there is usually a leucocytosis of 12,000 to 15,000 per cmm and an absence of eosinophils.

The urine shows the characteristics that are usually associated with high fever, and often some albumin but there are seldom casts or other evidence of nephritis.

### SYMPTOMATOLOGY

The incubation period is usually from 10 to 14 days, extreme instances of incubation periods of 4 and 24 days have been reported.

After a day or two of prodromal symptoms, general malaise, loss of appetite, headache, and joint pains the onset is sudden with the fever rising to its peak, 104°F or higher, in 48 hours, occasionally with a rigor. This is accompanied by pains in the loins and joints, severe headache,

offensive and there is o extended fingers and fibrillary twitchings of the face and the speech is hesitant slow and slurred Vomiting is common and constipation is a constant symptom The pulse is full and soft usually about 100 per minute and the blood pressure is low

Nervous symptoms develop early, the patient is drowsy and apathetic and during consciousness cerebation is slow as early as the fourth day (cf typhoid in which the mental symptoms develop much later) and become stupor coma

The temperature as noted above rises rapidly to 104°F and remains as a high remittent temperature for 10 to 12 days at the end of this period it may show deep remissions and eventually it falls by rapid lysis The whole febrile period lasts from 12 to 17 days

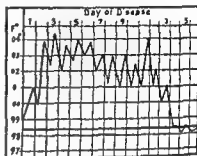


Figure 70 Temperature chart in a case of classical typhus (original)

develop for a few days and they may become petechial or even hemorrhagic and elbow and on the feet and at the fall of the temperature the skin that remains for some time

**Variations from the normal**—The disease described by Brill in 1898 and shown by Anderson and Goldberger in 1912 to be a form of typhus has

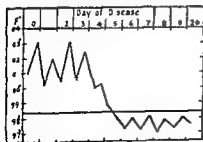


Figure 71 Temperature chart in a case of mild classical typhus which was diagnosed as broncho pneumonia but later shown by the Weil-Felix reaction to be typhus (original)

more recently been shown by Zinsser to be almost certainly a manifestation of late relapse of classical typhus for he found that in nearly every one of the 538 cases of this disease reported between 1910 and 1933 in New York the patients were emigres from Russia or other European countries where typhus is frequently epidemic This is a clinically mild type of typhus with no mortality usually with a modified rash which may be absent but the serum gives the typical agglutination against proteus X19

Another modified form of the disease in which the clinical picture is

**Complications**—Broncho pneumonia is common, other complications are stomatitis, parotitis, and even noma, thrombosis followed by gangrene of the feet or toes, genitals, and ears characterize some epidemics. Heart failure, preceded by a very low blood pressure and a slow pulse, is not an uncommon mode of death.

### DIAGNOSIS

In a typical case, the clinical diagnosis will present little difficulty, the points which differentiate typhus from typhoid are (i) sudden and rapid onset with the early development of severe symptoms, (ii) pains in the joints, limbs, and loins, and rigidity, (iii) the rash, (iv) the nervous symptoms and especially their earlier development (v) the leucocytosis, and (vi) the earlier and more rapid resolution.

Of the laboratory methods, the Weil-Felix reaction is the most valuable. This test is dependent on the probably accidental similarity of the antigenic structure of the specific rickettsia of typhus to that of a bacillus of the proteus group, X19, that was originally isolated from the urine of a typhus patient and found to be agglutinated in a high titre by his serum. Though really a non-specific test, this test is as specific as any 'specific' agglutination test in common use. At the end of the first week, the patient's serum gives a positive result in a dilution of 1 in 100, and by the end of febrile period it may be as high as 1 in 5,000, agglutination persists for some weeks and probably for some years in a low titre, which may be raised by some other febrile attack. It is not

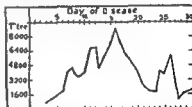


Figure 72 Graph based on the Weil-Felix reactions on 85 samples of serum from definite cases of typhus taken at different periods during the disease (original)

More recently, an agglutination test with an emulsion of rickettsiae has been developed but this test presents no advantages in this form of typhus.

Of the more elaborate laboratory procedures guinea pig inoculation is the most useful, about 2 c.c. of the patient's blood during the febrile period is inoculated into the peritoneal cavity of a guinea pig. The animal is kept in a dark, cool place and its temperature is recorded daily. In 2 to 3 days the animal becomes ill and dies. The blood is then removed and the Weil-Felix reaction is performed. A positive result is indicated by a high titre of agglutination. This test is not specific for typhus but is a valuable aid in the diagnosis of this disease.

## PREVENTION

In the face of an epidemic the first duty of the doctor is to protect his medical personnel, and incidentally himself. The danger comes from louse infestation, contamination from squashed lice and lice-fæces, and from inhalation of dried lice-fæces. A measure of special importance in this disease is the protection of medical personnel with masks, those dealing with dirty dry clothes should wear gas masks. For other details of anti-louse measures, see above (p. 231).

A great deal of attention has been paid to the subject of prophylactic inoculation during the last quarter of a century even when the prospects of producing a vaccine for wholesale inoculation seemed very remote on account of the obvious desirability of protecting medical personnel and laboratory workers. Weigl (1924) produced the first successful vaccine from trituration of the intestines of infected lice, this method had very obviously a limited application. The two methods that now promise success are those of Zinsser and his co-workers (1937) who have produced vaccine on a large scale by the combined agar tissue culture and a yolk sac culture methods, and of Durand and Sparrow (1940) who have produced a vaccine by inducing massive lung infections in mice by insufflation of rickettsiæ. In animal experiments and for the protection of individual workers subjected to special risk, they have been successful but at the time of writing neither of these methods has been put to the practical test of the protection of large populations during epidemics, however it is probable that ample opportunities will soon arise in Europe if not elsewhere.

We have certainly reached a stage where medical personnel might well be protected in this way, but at present in most circumstances the protection of a whole population by this means would be too expensive.

## TREATMENT

The treatment is almost entirely symptomatic. Convalescent serum has been used but has not yet established any reputation. The production of antiserum on a large scale has not yet been undertaken, but this may be possible now that the difficulty of getting rickettsial vaccine has been largely overcome.

The patient must of course be kept strictly in bed throughout the fever and for some days after defervescence, and given a balanced diet, mainly fluid, with plenty of additional fluid to drink, the course of the disease is comparatively short, and it is not therefore so necessary to maintain a high calorie diet, as in the case of typhoid, but in milder cases it is advantageous to do so. Hydrotherapy should be adopted to keep the temperature down, and strict attention should be paid to mouth hygiene and to the skin, particularly pressure points, which should be rubbed well with alcohol. The bowels should be moved by a mild laxative given nightly and, if necessary, by an enema given every second day.

In very dehydrated and toxic cases, intravenous saline has been used with success, in toxic cases, intravenous glucose (5 per cent) is also useful.

A sedative will often be necessary, phenobarbitone should be tried first and then codeine, but, if neither is successful, it may be necessary to resort to morphia. A lumbar puncture will sometimes relieve extreme restlessness. Frequent small doses of brandy are very useful, and cardiac

stimulants may be necessary, camphor in ether or cardiazol is preferable to strychnine or digitalis. Oxygen will often be useful.

### PROGNOSIS

The death rate is very variable and will depend on the conditions, for example, in time of famine and amongst half-starved and exhausted refugees it may be nearly 100 per cent, it will also vary from epidemic to epidemic but is seldom less than 10 per cent, in children the rate is low and in the aged high. Death usually occurs about the 10th to 12th day.

## TRENCH FEVER

**Definition**—Trench fever is a febrile disease of moderate severity which shows a tendency to relapse, it is caused by a rickettsial organism, *R. quintana*, which is transmitted to man sporadically from the louse in which it is a saprophytic infection. The disease appeared during the last war, mainly in the trenches on the western front, but also in Poland, Northern Italy and Macedonia, and has subsequently disappeared.

**Ætiology**—The causal organism, *Rickettsia quintana*, is apparently a natural parasite of the louse, *Pediculus humanus*, and only infects man sporadically. This rickettsia lives in the lumen of the gut of lice, and is never intra-cellular, its normal cycle is from louse to louse by contamination and only when he is subjected to intensive dosage with the virus does man become infected. The infection is transmitted from the crushed bodies of lice or from their feces, through an abrasion in the skin or via the conjunctiva. Man is said to be infective to the louse from the third day of the disease, and to remain so well into convalescence but the early experimenters who demonstrated this do not seem to have dealt with it.

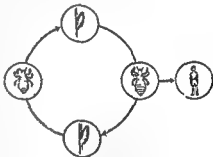


Figure 73 Suggested transmission cycle in trench fever

The relation between *R. quintana* (and *R. weigli*, vide infra) and *R. pediculi*, the natural rickettsia of the louse, is not clear. These two rickettsias are indistinguishable, both morphologically and in their relation to the louse, as they are both extra-cellular and non-pathogenic in the louse, but the latter is normally non-pathogenic to man. It seems possible that, in certain circumstances not yet determined, *R. pediculi* becomes pathogenic to man. As this disease has now disappeared, quite possibly only temporarily, it is impossible to study it, and the rickettsial organism that causes it, by modern methods.

Weigl's disease, which is the name given to a localized laboratory outbreak of rickettsial infection, is almost certainly exactly the same disease, laboratory workers were infected through handling infected lice

**Symptomatology**—The incubation period is eight to ten days. The onset is sudden, usually without prodromal symptoms, but occasionally there is headache, weakness, restlessness and diarrhoea. In a few cases the onset is so sudden that the patient falls down, or becomes so giddy that he cannot walk, other symptoms are generalized pains, vomiting and gastro-intestinal symptoms. The temperature rises to 103°F, or so, and the fever continues for about three days, it then falls to normal for a day or two and again rises. The periodicity

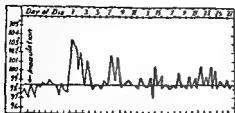


Figure 74 Temperature chart in trench fever (after Byam 1923)

varies between four and eight days. There is usually conjunctival injection, a very dirty tongue, occasionally rose spots on the chest, that disappear on pressure, and a slightly enlarged hard spleen. The blood shows a moderate leucocytosis. The diagnosis is largely clinical and circumstantial, and by a process of exclusion. At the present day, it would be unwise to make this diagnosis in the absence of a heavy infestation with rickettsia-infected lice.

**Prevention and treatment**—The louse is the essential factor and vigorous measures, indicated above, should be directed against this parasite. Treatment is symptomatic.

## MURINE TYPHUS

**Definition**—Murine typhus is a fever of the typhus group, of moderate severity, caused by *Rickettsia muricola* (mooseri) which is closely related to, if not identical with, *Rickettsia prowazeki*, and is transmitted to man by the rat flea, *Xenopsylla cheopis*; it occurs endemically in many tropical and sub-tropical countries.

**Synonyms associated diseases and geographical distribution**—Included under this heading are *tabardillo*, or endemic typhus of Mexico and the south-eastern states of the U.S.A., ship typhus of Toulon (France), idemic typhus, and certain parts of the world, Syria,

## ÆTIOLOGY

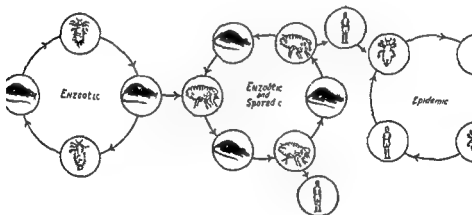
The causal organism is usually known as *Rickettsia muricola*, but is also referred to as *R. mooseri*, *R. prowazeki*, and in its behaviour to it, in the flea, it is found in the gut, but it does not kill the insect. It is that *R. muricola* produces scrotal swellings when inoculated intraperitoneally into guinea-pigs, but some doubt has been thrown on the stability of this differentiation by the observation that *R. prowazeki* will acquire this characteristic if it is transmitted through a series of guinea-pigs.

**Transmission**—The epidemiological investigations of Maxcy (1926), the later experimental work of Dyer *et al.* (1931), and the co-ordinating studies of Zinsser and his associates have led to a clearer understanding of this disease. These studies have established the following facts. The

main reservoir of infection is the rat (mice and other rodents also possibly act in this capacity), and the infection is passed from rat to rat by the rat louse *Polonyxenus*. This louse is specific to the rat and does

the rat and man is very close. (Compare the transmission of plague by the same rat flea: in this case the rat dies, the infected fleas leave the dead rat to find new hosts, either rats or man, and a rapid dissemination of infection takes place, resulting in an epidemic.)

Further, it has been shown that from man, the louse can acquire the



This demonstrates how the virus of typhus survives during the inter-epidemic periods, and seems to offer a very reasonable explanation for the apparent spontaneous generation of epidemic typhus.

Zinsser has pointed out that the facts of the non pathogenicity of this rickettsia to the flea and its lethal effect in the human louse, suggest a much longer association with the former or in other words that endemic murine typhus was the older disease from which epidemic typhus originated.

**Epidemiology**—The disease is sporadic. It occurs where man lives in close association with rats: in insanitary prisons, in crowded and insanitary barracks of tropical ports, on rat-infested ships, and in grain stores.

In the endemic areas, the incidence of this disease may be such as to constitute an important public health problem, and even in the United States, the annual incidence is in the neighbourhood of 3 000, with a death rate of about 3 per cent.

In most of the endemic areas, it has no special seasonal incidence, but, in the colder countries where it occurs, it is a summer or autumn disease. Individuals of all races and ages and both sexes seem to be equally susceptible.



The relation of this disease to epidemic typhus has been suggested above. When once the louse-man cycle has been established the disease takes on all the characters of classical typhus.

**Pathology.**—This does not differ materially from that of classical typhus, but it has not been studied very thoroughly as deaths are comparatively rare.

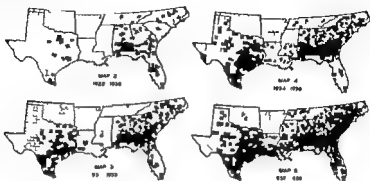


Figure 76 The extension of murine typhus in the southern states of the U S A (H E. Melency *Amer J Pub Health* 31, 219)

**Symptomatology**—The disease differs from classical typhus mainly in its intensity. The incubation period is from 10 to 16 days, the onset is sudden and may be quite severe, but the severity is short-lived and the temperature drops to the 100°F line or so within a few days, the whole course is not usually more than 10 to 14 days. The rash appears about the fifth day, but is less intense. The deaths are usually due to complications, e.g. broncho-pneumonia but occasionally an isolated case runs a severe course which may be indistinguishable from the classical disease on clinical grounds.

The diagnosis is confirmed by a positive Weil-Felix reaction with the OX19 antigen (*vide infra*).

**Immunity**—It is on the immunological experiments that our knowledge of the close relationship of the murine and classical typhus depends. In animals, previous infection with either virus produces a solid immunity against infection with the other, this lasts in some cases up to a year. Whilst complement-fixation tests confirm the existence of this cross-immunity, quantitative experiments show that a positive result will occur in higher dilutions with the homologous than with the heterologous rickettsia.

Both rickettsial infections lead to the formation of agglutinins against proteus OX19 in animals and man.

There is no cross-immunity against the other species of rickettsia.

**Prevention and treatment**—It must be obvious that the preventive measures in this disease are on entirely different lines from those in epidemic typhus. The main attack is on the rat, but it is obviously essential that the rat's fleas must also be destroyed, or they will migrate to other rats and possibly man, and will tend to disseminate the infection. The methods to be adopted are numerous and varied, and will depend very largely on the circumstances (*vide PLAGUE*).

One could not advocate extensive and expensive measures for the sake of limiting this disease alone but rats carry so many other diseases and cause so much economic loss through their rapacious and destructive habits that any successful measures against these vermin must be a sound investment.

The dangers of heavy louse infestation in areas of endemic typhus are worth stressing again here for even if other circumstances are necessary for the change over to the epidemic form to take place louse infestation is a *sine qua non*.

Personal prophylaxis can be effected by inoculation with either the murine or the classical strain.

Treatment is symptomatic, on the lines indicated above.

### ROCKY MOUNTAIN SPOTTED FEVER

**Geographical distribution.**—As the name suggests the disease was first recognized in the Rocky Mountain region of the United States, particularly in the states of Colorado, Utah, New Mexico, Arizona, and California. It has since been reported from Virginia, North Carolina and Washington D.C. but a few cases have been reported from nearly every state in the union outside of New England. Wisconsin and Michigan. In Canada it has been reported from British Columbia and Alberta.



Figure 77 The distribution of Rocky Mountain Spotted Fever in 1941 (E. C. Faust 1944)

The typhus of Sao Paulo and Minas Geraes of Brazil and Tobia fever in Colombia are apparently the same disease. Fièvre boutonneuse which occurs in France, Portugal, Roumania and North Africa, Kenya typhus and the tick bite fever of southern Africa are closely allied diseases.

### ÆTIOLOGY

**The virus.**—The causal organism was originally named *Dermacentrozoon rickettsii* but was later shown to be a rickettsia and re-named *Rickettsia rickettsii*. It has the morphological and tissue-cultural characters of other intra-cellular rickettsiae but is distinguished by its intra-nuclear position. It occurs in nature in the wood tick and

in other ticks. Many wild rodents as well as laboratory animals can be infected and in the guinea pig it produces fever and the characteristic scrotal lesion (Neill Moose reaction).

**Transmission**—The two principal transmitters are the wood tick, *Dermacentor andersoni*, and the dog tick, *Dermacentor variabilis*, the former is the main transmitter in the mountain states and the latter in the

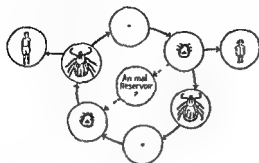


Figure 78. Transmission cycle in Rocky Mountain spotted fever (Western variety).

eastern states. In the southern states, *Amblyomma americanum* has also been found infected in nature and is probably a vector. Many other ticks are potential vectors. In Brazil, *Amblyomma cajennense* is the tick incriminated, and in France the dog tick *Rhipicephalus sanguineus*.

It is often stated as a definite fact that wild rodents and certain small carnivores, jack-rabbits, chipmunks, porcupines, weasels, etc., con-

stitute a reservoir of infection. Though none of these animals has been found infected in nature in the endemic areas, many are susceptible to the infection and it seems probable that they help to maintain this widespread sporadic infection. It has however been pointed out that no reservoir is necessary, since the infection is transmitted to the progeny of the ticks in the case of the main vector, *Dermacentor andersoni*, through an infinite number of generations.

The adult ticks bite man and transmit the disease to him, and the nymphs and larvae will sometimes be found on children. The percentage of ticks infected is comparatively small, in the enzootic areas this varies from place to place, and from year to year in the same place, but the general average is about 2 per cent, and it seldom rises above 10 per cent of a sample of ticks examined.

In a starved tick the infection is dormant and it takes some time before and that starved infected tick has been fed on a susceptible animal for as long as three days, without transmitting the infection. The infection is transmitted by the bite of the tick and by squashing infected ticks.

**Immunity**—The immunity produced by an attack is not complete and many instances of second attacks have been reported. There is no cross-immunity with other forms of typhus except those that have been recognized as closely allied diseases (vs). The serum agglutinates proteus OX19 and OX2, but in rabbits, the Rocky Mountain spotted fever strain will give rise to agglutinins against OX2, whereas the typhus strain will not. Some immunity can be produced by inoculation with a vaccine.

**Epidemiology**—The incidence is sporadic. In the mountain states, it is to some extent an occupational infection, in that those engaged in hunting and trapping game and rodents, and in agricultural pursuits, are most

likely to be infected. Others that are frequently infected include prospectors and miners, highway construction workers, and tourists and picnickers. Thus, men are most frequently infected in these areas, but in the eastern states where the dog tick is the carrier, the tick is brought into the houses, and women and children are more frequently infected.

The intensity of the disease in the Bitter Root valley has been as high as 80 per cent in the mountain districts, eastern states, where *Dermacentor variabilis* is the transmitter, it is much lower, and the average death rate is probably less than 25 per cent. The lower death rate in the eastern states is certainly in part, and possibly entirely, due to the lower age-incidence in these states (Topping, 1943). The severity varies from year to year in any one area.

**Pathology**—The rickettsiae invade the endothelial cells and also the muscular coat of the smaller blood vessels so that thrombo necrosis is the reaction rather than proliferative endarteritis. Of the macroscopic lesions extensive ecchymoses into the skin, mucous membranes, and serous cavities, enlargement of the spleen, meningeal congestion, broncho-pneumonia and scrotal gangrene are common.

In the blood there are no characteristic changes, there is usually a moderate leucocytosis, but a leucopenia (granulopenia) is not uncommon. The urine is acid, it is often reduced in amount and retention may occur. Some albumin may be present.

### SYMPTOMATOLOGY

The incubation period is from three to twelve days, being shorter in the more severe infections, after a day or so of prodromal symptoms,

*supra*)

The temperature rises by rapid steps to a maximum between 103°F and 106°F, according to the severity of the attack, in five or six days, it maintains its height for a few days often with deep remissions, and then begins to come down by lysis, taking three to four days in the eastern type and seven to eight in the more severe western type, the whole febrile period lasting from two to three weeks. Fatal hyperpyrexia with temperature above 108°F sometimes occurs.

The rash usually appears from the second to the fourth day, but may be delayed to the fifth or even sixth, and is sometimes preceded by a subcuticular mottling of the skin. The typical rash is bright red, macular or maculo-papular, it appears first on the wrist and ankle, sometimes on the forehead or back, it spreads rapidly all over the body including the palms and soles. In severe cases it commences with small pin-head spots

that rapidly darken and eventually become hæmorrhagic and coalesce. In the less severe cases the spots appear in a succession of crops at a few days interval. The rash fades slowly leaving a brown stain which is very photosensitive becoming red on exposure and sometimes pock marks.

The pulse is full and bounding and often disproportionately slow in the mild cases but in the toxic cases it becomes very rapid and is often uncountable.

Convalescence is usually slow and it may take some months.

The common complications are pneumonia, phlebitis and hæmorrhages including cerebral rarely and less frequently iritis and acute nephritis.

Sequelæ are not common but neuroses, psychoses and insomnia, deafness, impaired vision, anæmia and myocardial weakness have been reported.

Diagnosis does not present any difficulties in a typical case but the temperature may suggest typhoid, other conditions that will have to be considered are measles and other acute exanthemata, secondary syphilis, meningitis and purpura hæmorrhagica.

Further evidence will be obtained from the Weil-Felix reaction, standard OX2 at 1 in 320 or higher should be complement fixation test will confirm the disease from the other rickettsial fevers and tsutsugamushi but not from

#### Sao Paulo and Tobia fever

Another laboratory test is the inoculation intraperitoneally into a guinea pig of 1 c.c. of blood taken from the patient during the febrile stage. In the severe types there is a characteristic scrotal swelling which may lead to gangrene but in milder types this may be fleeting or absent. There is always some febrile reaction and often the guinea pig dies. Death does not follow other rickettsial infections.

Prevention and treatment—Personal prophylaxis includes protection against tick bites by means of suitable clothing for example riding breeches and boots, women should wear similar clothes. When there has been any chance of tick infection the lower limbs and body should be touched with a 10% solution of picric acid or pure means.

infection may be obviated.

In the districts where the dog tick is the carrier dogs should be washed in some insecticidal solution to prevent ticks adhering to them whenever they have been out hunting and the inadvisability of allowing them to come into the house at all is obvious. Great care should be exercised in removing ticks from dogs as several persons have infected themselves by this means.

Vaccination has now been practised for a number of years and it has been shown that some considerable degree of protection is given. However it is obvious that there is room for improvement in the vaccine for many inoculated persons have died as the result of infection with the virulent western strain. This is probably largely a matter of dosage and with the improved technique of the last few years a better vaccine should be forthcoming. Re-vaccination each season is advisable.

**Prognosis**—This has been discussed above. The main factor is apparently age. In children the death rate is low and in the elderly and middle aged it is always high.

**Treatment** is symptomatic and does not differ from that of classical typhus. No known drugs are of any value.

### ASSOCIATED DISEASES

Associated diseases include the tick bite fever of southern Africa, the *phallos* which s have *phallos*. In the last named hereditary transmission for a number of generations has been proved. The reservoir of infection if such exists is presumably a veldt rodent and cattle and dogs act as conveyors of ticks to the vicinity of man. The infection is transmitted by the bite through an abrasion or into the conjunctiva in the latter case from contamination from a squashed tick. Clinically it is usually a mild infection with a low death rate less than 1 per cent. There may be an initial lesion of the *tache noire* type and there is usually a rash about the fifth day. The fever lasts about 14 days and ends by rapid lysis. In elderly patients femoral thrombosis appears to be a common complication, pulmonary thrombosis has also been reported. The Weil Felix reaction shows a late development—after the 10th day—and is positive with OX2 and OX19 antigen in moderately high titre the former being higher than the latter usually (*vide* Gear 1940).

*Fievre boutonneuse* (*vs*) which occurs in the south of France and along the north African coast is caused by *Rickettsia conori* which is probably identical with *R. rickettsi*; it is transmitted from the dog which may act as a reservoir of infection by the dog tick *Rhipicephalus sanguineus*. It is a comparatively mild form of typhus with a low mortality (2 per cent); there is an initial lesion—the *tache noire*—which is similar to that of tsutsugamushi disease (*vs*) but antigenically the disease is more closely related to Rocky Mountain spotted fever. The serum agglutinates proteus OX19 and OX2.

In Sao Paulo typhus of Brazil the infection is transmitted by the tick *Amblyomma cajennense* possibly from a rodent reservoir. It is a severe disease with a high mortality (70 per cent) and similar both clinically and antigenically to Rocky Mountain spotted fever.

### TSUTSUGAMUSHI

fever is a disease of transmitted to man by from field mice rats at lesion and adenitis

and it runs a severe course the serum of the patient agglutinates the proteus organism OXK.

the pseudo-typhus of Sumatra are certainly the same disease is also reported from Indo-China and the Philippine

### ÆTIOLOGY

The virus — The causal organism is *Rickettsia orientalis* or *R. tsutsugamushi*. This species is far more refractor propagation than the other species of rickettsia. Infection only with considerable difficulty in guinea-pigs, after lower resistance, but admitted to monkeys and dermal inoculation. In the latter it produces a ulcer, a leucopenia, against O.

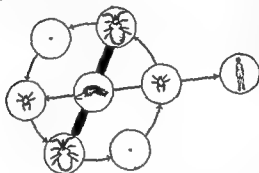


Figure 79 Transmission cycle in tsutsugamushi disease

*Laelaps australiensis*. The larval mites, which only become infected from field rodents, (eg in Japan *montebelli*), transmit the infection to their offspring, of the next generation pass it on to man by their infection). The small mite, measuring only 0.25 mm to the naked eye, and being easily overlooked, remains for days. The infection from this small insect is a venereal lesion in certain cases indicates that sometimes proboscis reaches the deeper layers of the skin, is

Immunity — Cross-protection tests with guinea-pigs show complete reciprocal cross immunity and the Japanese type of tsutsugamushi, but not typhuses. The specific proteus is the OXK.

Epidemiology — The disease is an endemic presence of the reservoir of infection and the transmission almost exclusively amongst farmers and other field wardens and hunters. In Malaya, practically all have been in the habit of walking through the long lalo workers on oil-palm estates, especially those who of the trees where rats forage for food.

The disease occurs mainly amongst adult occupational associations, but probably for no reason amongst children doing similar work, persons especially susceptible but the initial lesion and the

hæmorrhages in two cases, 11 enlarged spleens of which eight were diffuent, enlarged lymphatic glands in 10, and petechial hæmorrhages in the heart in four, in the pleura in 11, and in the kidneys in five cases

The blood shows a leucopenia or a normal leucocyte count, very rarely a slight leucocytosis. There is an actual or relative increase of lymphocytes, a slight increase of monocytes, a granulopenia and usually complete absence of eosinophils. The urine shows traces of albumin, and the usual characters associated with fever.

### SYMPTOMATOLOGY

The incubation period in this infection varies over a wide range, from 5 to 21 days. The onset is usually sudden, all symptoms developing within 24 hours, but occasionally there is a prodromal period lasting a few days with a slight headache and malaise, the first definite symptoms

develop

The initial lesion that occurs at the site of the bite was at one time the basis for the diagnosis of this form of typhus, but

and Sumatra it is apparently very common, in Malaya it is rarely found. The lesion is at first macular then papular and eventually a necrotic centre develops which separates and leaves a punched out ulcer. It is very probable that

in a number of cases it does not go beyond the macular or papular stages and heals before the main symptoms develop. That it is noticeably more common in fair-skinned individuals adds support to this suggestion

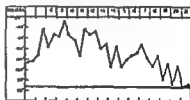


Figure 80 Temperature chart in Malayan VK typhus with an initial lesion (see plate V figure 4)

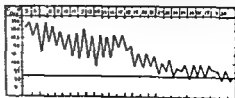
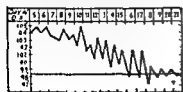


Figure 81 Temperature charts in tsutsugamushi disease (after Nagayo 1923)



The typical lesion at the time of onset of general symptoms is a depressed necrotic eschar about 1 mm in diameter with a well-defined areola of about the same breadth.

The fever usually rises rapidly to 101 or 102°F, and then after a further few days reaches its maximum of 104° or higher, and is maintained at this level with deep morning remissions of two or three degrees, until the end of the second week, when it falls by rapid lysis, after this there may be one or two final kicks in the temperature chart up to 100° or 101°, during the next day or so, before the fever finally subsides. In the Japanese type, the lysis may take several days and a low fever may continue for another week. As in other typhuses, the height of the fever is not a guide to the severity of the infection.

The pulse rate is usually increased with the temperature, though a few cases in which it remained slow have been reported, in convalescence there may be bradycardia.

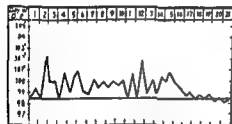


Figure 82 Temperature chart of a case of scrub typhus in Malaya (Anigstein, 1933)

The lymphatic glands, especially but not only those that

and tender

Nervous symptoms are usually pronounced, and develop as the temperature rises, there are fine tremors of the lips and tongue, and twitchings of the face muscles, the patient is dull and apathetic

during the day and often delirious at night, insomnia is common, he may become stuporous and eventually pass into coma. Another symptom is deafness, this is irregular but tends to develop throughout the disease.

**Complications**—The only frequent complications are bronchitis and broncho-pneumonia.

lesions or even of the remains of nosis of this type of typhus though teristic clinical feature, others are with an increase in lymphocytes

The Weil-Felix reaction gives agglutination in high titre against proteus OXK, and a negligible agglutination with OX19 and OX2. The lowest titre that can be accepted as diagnostic is 1 in 250, but, as a few cases of leptospira proteus, demonstration can be obtained refractory

If mice are inoculated intraperitoneally with the supernatant fluid from a blood clot ground up in saline they will die within 16 days and show abundant rickettsæ in their peritoneal membrane

**Prevention and treatment**—The adoption of suitable clothing when in endemic areas and careful inspection of the body after removing the clothes are obvious measures for personal protection. Prophylactic inoculation is being developed for this as well as for other typhuses. In special circumstances rodent extermination may be advisable where the specific reservoir has been identified but such a measure should not be advocated lightly

**Prognosis**—The infection is less severe in children and very fatal in old people. In Japan the death rate is given as 30 to 60 per cent and in Malaya as an average of 15 per cent

### Q FEVER

The most recent recruits to the typhus fevers are the so called Q fever first reported from Brisbane (Derrick 1937) and the American Q fever which takes the form of a pneumonitis. These two diseases appear to be caused by antigenically identical rickettsiæ

The Australian disease is confined almost entirely to abattoir and dairy workers except that many laboratory infections have occurred

The Queensland bandicoot *Isodon torosus* provides a reservoir of

that still have to be confirmed especially with regard to the part played by *Ixodes holocyclus* but it would appear to be as shown graphically below —

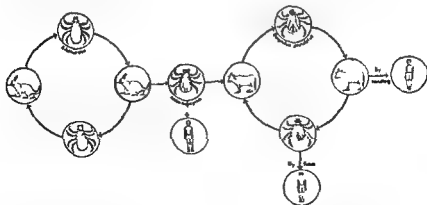


Figure 22 Probable transmission cycles in Australian Q fever

The causal organism *Rickettsia burneti* infects the endothelial cells lining the alimentary canals of the susceptible ticks. The rickettsiæ

multiply in these cells which eventually burst into the lumen of the alimentary canal, and the rickettsiæ are passed out with the fæces

Infection may take place by the handling of the cattle harbouring infected ticks from the tick fæ-  
epidemiological evidence that  
from the infected dust of the  
in casual visitors to abattoirs)

The infection is transmissible to guinea pigs monkeys and other domestic and laboratory animals but mice appear to be most susceptible and from their livers and spleens large numbers of rickettsiæ can be recovered with which agglutination tests can be carried out

Immunity develops in an infected person or animal and their serum will agglutinate the rickettsial emulsions There is cross immunity against the rickettsia that causes American 'Q' fever but not against any other rickettsia e.g. *R. rickettsi* or *R. prowazeki*. No agglutination occurs with any of the recognized proteus X strains

The clinical picture is that of a mild form of typhus with a low mortality in the typical case the onset is sudden the fever rises to as high as 104°F with deep remissions it lasts for about a week and then falls by crisis There is another form in which the fever runs a more chronic course other symptoms are intense persistent headache photophobia and conjunctival congestion There is usually marked bradycardia There is no rash

The American form of Q fever has an interesting history in that it was an example of a disease in which the causal organism was discovered before the disease A rickettsia which was antigenically different from

Mountain spotted fever  
the tick *Dermacentor*  
outbreak of pneumonitis  
being experimented with  
ith pneumonitis who had  
ks

In the case of the laboratory infections many persons of whom one died who had had no direct contact with the cultures or infected animals were infected so that it seems probable that the infection was air borne possibly spread by dust

The causal organism of this American Q fever was called *Rickettsia diaporica* but it has been shown to be antigenically identical with *R. burneti* which has precedence

The position of this disease vis à vis other typhuses is not yet clear  
other features common  
usal organism though a  
size in its pathogenicity

## TYPHUS FEVER IN INDIA

A point was first drawn to this disease in India by  
typhus like fever that had occurred  
the clinical similarity between the  
and he strongly suspected that the  
if the patient) The importance of

this observation will be realized if we remember that at this date no form of tropical typhus had been recognized as such, and little was known about any of the non epidemic typhuses. Megaw later described other cases of typhus occurring in India, in which the patients had been bitten by unidentified ticks, in other cases, though there was no direct history of a tick bite, the possibility could not be excluded.

Since this date, a number of cases of typhus and suspected typhus have been reported from various parts of India. The most important publication on the subject is that of Boyd (1935) who collected data from 110 cases that had occurred in the army, or in persons associated with the

any of the previously recognized insect vectors were involved

ution has  
ned with  
blood of  
isolation  
vectors

Competent research workers have been engaged in these investigations and the inconclusive results that have been produced are due to the circumstances, mainly the extremely sporadic nature of the disease in this vast country, though the annual incidence probably runs into tens of thousands

n isolated from  
rat fleas, and a  
The monkeys  
a reservoir of  
*bicula deliensis*,  
dilution of 1 in

50 in 32 per cent of instances and at a dilution of 1 in 25 in nearly all others, whereas the plains monkeys not so infested give a much lower grade of agglutination

The only possible view to take of the position is that in a vast country like India, with almost every possible climate represented it would be very surprising if there were only one type of typhus. A more reasonable hypothesis is that each of the major groups is almost certainly represented. Our object should be to sort them out and attribute to each its special clinical picture, its vector, and its reservoir of infection so that they can be recognized and appropriate measures of prevention can be adopted rather than to stress their similarity—beyond the fact that they are typhus fevers—and to claim for them homogeneity.

The fortunate accident of the close antigenic relationship of the different rickettsiae to certain specific strains of proteus will serve us for the time

greater extent than they have been in the past, by investigators in India. Meanwhile, it is important that clinicians should make themselves familiar with the clinical pictures in the different types of typhus that occur in other countries, so that they will recognize them when they encounter similar diseases in India, and that bacteriologists should include the proteus group of organisms in their Widal tests, even when physicians do not ask for this test specifically.

**Classification**—At the present date, Boyd's classification of the typhuses of India is the only one worth quoting, this classification has its strict limitation, as Boyd would be the first to admit, and it is to be hoped that it will soon be replaced by a more satisfactory one. Boyd's classification with certain important clinical and other data is given in the table below —

TABLE V

Type	VK	V2	V19	
			Poona Ahmed-nagar	Bangalore
<i>Geographical distribution</i>	Northern Eastern and Southern Commands except Poona Ahmed nagar area and Madras District Not reported from Western Command	Deccan District and Poona Independent Brigade Area only	Deccan District C P and Poona Independent Brigade Area only	Southern Command except Poona Independent Brigade Area and Ahmed nagar vicinity
<i>Seasonal incidence maximum months</i>	August and September	December	December	More or less evenly spread except February March and April
<i>Rash —</i> Number of cases	<i>British</i> 15/21 <i>Indian</i> 1/14	8/8 5/6	10/10 6/6	5/6 1/21
<i>Day of appearance</i>	<i>British</i> 5th or 6th <i>Indian</i> 7th	3rd or 4th	3 d	4th to 10th 8th
<i>Type</i>	Flush macules	Macules papules petechial	Macules papules petechial	Maculo-papular
<i>Distribution</i>	Trunk only	Generalized	Generalized	Trunk and limbs
<i>Duration in days</i>	<i>British</i> 7 <i>Indian</i> 1	18.4 14.4	25 10.5	4 3
<i>Staining</i>	Nil	In some cases	In some cases	
<i>Average duration of pyrexia in days</i>	14.2	12.5	15.5	10.4
<i>Average stay in hospital in days</i>	31	27.5	29.5	24.6
<i>Proteus agglutinins</i>	<i>VK</i> +++ <i>V2</i> — <i>V19</i> —	± +++ +	± ± + to ++	± ± +++

Epiderm - In most of Negroes' hair there was a clear evidence of  
tion with  
in many ( )  
developed  
time Many reports recently received have been of cases amongst town  
residents

It would not be advisable to attempt to correlate the above descriptions with the physical descriptions given in this case as follows —

The first symptoms were malaise and headache, which gradually increased until the fourth day. The headache was referred to the orbits just above the eye-balls and from the fourth day it steadily subsided. The only other symptoms were weakness and some pain and discomfort in the muscles of the back which caused disturbance of sleep for two or three nights.

On the fifth day a diffuse macular erythema was noticed all over the body including the palms and soles and the face. In the neighbourhood of each spot there was at first swelling and tenderness of the skin so that flexion of the fingers was painful.

In a day or two the eruption became more pronounced the colour changing to brownish red about the eighth day the spots had a distinct tendency to be petechial and by this time the swelling and tenderness had disappeared. The eruption faded rapidly with the fall of the temperature but a brown staining at the site of the spots was visible for about five weeks afterwards.

On the front of the right thigh where the spots were readily observed and

There were no symptoms referable to the respiratory or nervous system and the patient took a keen interest in the progress of his case. Convalescence was rapid; he got up from bed on the day on which the temperature fell to normal and ten days later was in his usual good health.

The leucocyte count on the tenth day was 15 400 per c.mm.

Boyd (1935) described the clinical picture of the most important group, **XK**, in his classification, as follows —

Severe headache was a very constant and early symptom. The face was usually flushed and the conjunctivae somewhat injected. Rigors and sweats were common in the early stages and toxæmia with its accompanying symptoms of lassitude and drowsiness was of varying severity. Severe pains in the joints or "all over the body" occurred in several cases.

The rash was by no means a constant feature being present in only 11 of the 21 British cases and in only 1 of the 14 Indian cases. It usually appeared on the fifth or sixth day but was recorded as early as the first and as late as the eighth day of illness.

The rash appears on the fifth day of the disease. A flush may be present on the fourth day. This may be demonstrated on an apparently normal skin by the pressure of the hand. The paler impression produced by the palm and fingers persists on the skin. The rash is that of true typhus though the lenticular papules have not been observed. It is a dusky erythema with scattered irregular blotchy underlying macules purple in colour. The macules persist on pressure in some degree, while the flush fades leaving the skin very pale by contrast.

The rash is raised but cannot be felt. The distribution of the rash is wider, it is on the upper part of the front areas. It is particularly well seen on the upper and lower limbs but usually the face are not affected. It is not very striking in appearance and may not be noticed. It fades gradually the rash disappearing earlier than the macules. As a rule it is no longer visible at the termination of the pyrexia.

It is worthy of note that in no case of this series did the rash become papular or petechial nor, with one exception did the macules extend beyond the trunk. The macules were found chiefly on the abdomen and thorax, the face and neck and extremities were unaffected.

The inconspicuous nature of the rash no doubt affords the explanation of its apparent rarity in Indian patients as it is presumably obscured by the pigmented skin.

The average duration of the rash, calculated from figures given in thirteen cases, was seven days. There was however, difficulty in determining the exact time when it could be said to have disappeared.

Complications and sequelæ were by no means uncommon. Nine cases showed pulmonary symptoms, 5 developing bronchitis, 2 pneumonic symptoms and 2 pleurisy. Three cases developed acute mental symptoms, and 2 others varying degrees of transient paralysis.

The average duration of fever (33 cases) was 14.2 days. During the pyrexial period the pulse rate was relatively slow, resembling in this respect the pulse in fevers of the enteric group.

Recovery was by lysis and in some cases by crisis. In uncomplicated cases all other symptoms disappeared and convalescence was rapid as soon as the fever subsided.

The average stay in hospital (35 cases) was thirty one days.

**Recent observations**—A few notes are added on three recent reports on outbreaks of Indian typhus fevers.

Heilig and Naidu (1942) reported 14 cases in Indians in Mysore, from the city and surrounding country. All the cases were sporadic, they occurred between August and February, and there were no indications

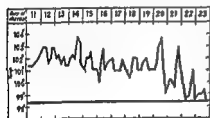


Figure III Temperature chart of a case of Indian endemic typhus

regarding the transmitting agent. The onset was sudden, but without rigor, with malaise, headache, photophobia, body aches and usually conjunctival suffusion. No splenic enlargement was noted. The temperature chart showed a moderately high remittent fever which lasted from 16 to 21 days and resolved by rapid lysis (see figure 84). The rash first appeared between the fifth and the tenth days, it started as a pinkish macular rash on the trunk and upper extremities, and it spread all over the

body, and to the lower part of the face in a few cases. The rash became maculo-papular, the pink colour changing to purplish, and then petechial, desquamation occurred during the fourth week, and, finally, it turned to brown and left a stain that persisted for months. There was a distinct leucocytosis in most cases.

The diagnosis depended on the demonstration of rickettsiæ in the tunica vaginalis of guinea-pigs injected with the blood of some of the cases but in only one case was a Neill-Mooser reaction produced in the injected guinea-pig.

The Weil-Felix reaction was positive with the OX2 antigen in most of the cases, though there was some co-agglutination with the other two antigens.

#### PLATE IX

Fig 1—Rash in epidemic typhus (Army Medical Museum)

Fig 2—Rash in Rocky Mountain Spotted Fever (Army Medical Museum)

Fig 3—Primary ulcer in a case of Malayan scrub (VK) typhus (after Fletcher and Field, 1929)



Fig 1

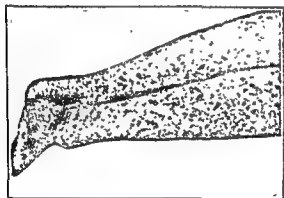


Fig 2



Fig 3





Fig 1—A case of Indian typhus (proteus agglutinations negative) 29th day of disease

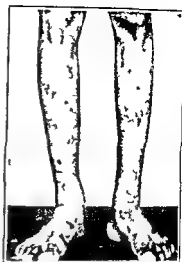


Fig 2—Same as figure 1



Fig 3—Rash in Indian typhus (after Heilg and Naidu 1941)



Fig 4—Neill Mosser reaction (after Heilg and Naidu 1941)

A second report was from a military hospital (personal communication from Lieut-Colonel T A A Hunter, R A M C). The patients were eleven British soldiers, who had been in camp near Bombay during the month of November, the symptoms developed in one case 17 days after arrival at the camp, and in another 111 days after leaving it, so that if infection took place in the camp—an almost inevitable conclusion—the incubation period was between 10 and 17 days, but there was no history of tick bite in any case. Eight cases occurred in one battalion.

The onset and the course of the disease was very similar to that of the Mysore cases, but the symptoms were exceptionally mild, the fever was also of the same nature and lasted from 13 to 16 days. The rash was also a marked feature in this series but developed within 24 hours of the onset of symptoms in every case and in two was the first evidence of the disease, it developed in the lower extremities first and spread rapidly all over the body except the face. This early development of the rash constituted the only striking difference between the two series.

The Weil-Felix was positive with the OX2 antigen in six cases, but in no case was a positive Neill-Mooser reaction produced in injected guinea-pigs.

These two series have a number of features common with Boyd's X2 group (see table V), but the difference in the time of appearance of the rash is interesting. There is no clue in either case to the transmission problem.

A third outbreak occurred in Calcutta in the autumn of 1942. The patients were again British

developed in nearly all of them. The temperature charts were very like the classical typhus chart,

but in one case with OX2

patients was house-infected

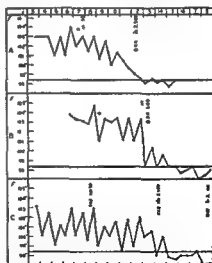


Figure 85. Temperature charts in three Calcutta cases of typhus.

Conclusion. The question in India is that we know that the disease is serious and we have to find out the extent of the problem. It is considered a serious public health problem. We have the example of the Calcutta cases. Typhus has apparently

increased ten-fold and Rocky Mountain fever has spread from the western states to the east coast. We must use the Weil-Felix test to help us to identify the disease, but we should be careful not to accept the indications of the test without clinical examination. The results may be that there are which one or

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# OROYA FEVER, OR BARTONELLOSIS

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very common secondary manifestation is the granulomatous eruption previously known as verruga peruana

*Historical*—It is believed that the fatal disease which wrought havoc in Pizarro's army in the 16th century was Oroya fever

Medical attention was first drawn to it in 1870 when during the building of the railway to Oroya 7000 deaths occurred amongst imported labour. It was from this that the disease received its name which is a misnomer as it does not actually occur in Oroya

In 1885 Carron a medical student inoculated himself from a verruga nodule and developed a fatal attack of Oroya fever. From this time local physicians have assumed that the fever and the subsequent eruption were manifestations of the same disease. The causal organism was identified by Barton in 1909 and his observations were confirmed by Strong and others in 1915

The ætiological identity of the two conditions was again questioned by the Harvard Commission in 1913 but Noguchi's cultural work re-established the claim for their identity and later Mayer Borchardt, and Kukuth (1927) produced both the local lesions and the severe febrile disease with anæmia, the latter after splenectomy, in monkeys by inoculation of material taken from a case of verruga peruana that arrived in Hamburg. These observations were confirmed by the Harvard Commission of 1937, in this instance cultures were used for producing infections in monkeys.

### EPIDEMIOLOGY

**Geographical distribution**—It has a limited distribution in South America between 2°N and 13°S. It occurs mainly in Peru, but recently indigenous cases have been reported from Bolivia, Ecuador and now Colombia. The area in Colombia is in the basin of the Guatara river, a fertile area with 100 000 inhabitants, the death rate from this disease in the first eight months of 1938 amounted to 1,800 persons.

**Other epidemiological features**—The disease is confined to certain valleys in the Andes, between 1,000 and 12 000 feet above sea level, in which sometimes every individual in the whole community is, or has been, infected. New-comers to these valleys almost invariably become infected and suffer the acute febrile attack, and frequently die.

The disease appears after the rainy season when insect life is most abundant and malaria is rife.

Persons of all ages are affected but the disease is much milder in children, and is probably often unrecognized.

### ÆTIOLOGY

**The causal organism**—*Bartonella bacilliformis* has two forms, a small bacillus like form  $1\mu$  to  $2\mu$  in length which may show branching and an ovoid form about  $1\mu$  in mean diameter. It stains well with Romanowsky stains taking a blue colour (see plate II F).

It can be grown in Vervoort's medium used for the cultivation of leptospira, but does not grow easily. It is suggested that the different strains of *Bartonella* vary in their ability to grow in culture medium.

They are found in the red cells in the peripheral blood in an acute case, and in the endothelial cells of the capillaries in post-mortem or biopsy tissue.

and muris, by the dog flea and the rat-louse, *Spilopsyllus*

**Sources of infection**—Man is probably the only source of infection. As bartonellæ are occasionally found in the peripheral blood in the absence of symptoms, or even some time after symptoms have subsided, it seems necessary to suggest an animal source. It is suggested that other wild animals are susceptible to the disease and may act as reservoirs of infection, though none have been found.

## PATHOLOGY

The general reaction produced is the result of bartonella invasion of the arteriolar endothelium and reticulo-endothelial cells of the lymphatic tissues, and of the blood destruction, much red cell debris has to be disposed of, and there is very great anæmia.

Lymphatic glands are often enlarged, and the spleen usually, and there is a deposition of dark-yellow pigment in most of the organs, which gives the reactions of melanin. There are often petechial hæmorrhages in the mucous membranes and in some of the viscera.

The endothelial cells of the arterioles and lymphatic channels are invaded by the bartonellæ, and the lumens of the channels are often blocked, so that necrosis or œdema may occur. Necrotic areas are often seen in the spleen, and also in the liver, in the central part of the lobules.

The bone marrow shows a marked hyperplasia, both of the erythroblastic and the leucoblastic elements.

In the local lesions there is blocking and dilatation of the vessels with the production of a hæmangiomatous condition. There is proliferation of the endothelial cells lining these blood sinuses, in these cells, bartonellæ may be found, but they are not numerous. There is much new blood vessel formation. The lymph channels are also obstructed, and the blocked vessels are surrounded by an area of infiltration, in which lymphocytes, plasma cells, and fibroblasts take part.

**Blood picture**—The red cell count may be reduced to less than a normal value, but the hæmoglobin is normal, as the red cells are on the whole normal.

The leucocytes will be increased, often up to 20,000 per cmm, the proportions of the various types being maintained at about the normal.

## SYMPTOMATOLOGY

**Discussion**—The view that Oroya fever and verruga peruana are manifestations of the same infection is now generally accepted. There is considerable parallelism between this disease and kala-azar, a condition in which an acute visceral disease may be followed by a generalized dermal eruption.

In Oroya fever, if the patient dies from the acute febrile disease, he naturally does not suffer from the dermal lesions. If he has a very severe attack, the infection may be stimulated, and in this case he will not have the dermal lesions. If he has a mild attack, he may have the dermal lesions to such an extent, that the bartonellæ within the endothelial cells in the skin and/or subcutaneous tissue will later multiply, and these will give rise to secondary lesions.

The initial attack may thus be (a) severe and fatal, (b) moderately severe, (c) mild or (d) asymptomatic. The secondary lesions will follow in (b), (c) and (d), probably in an ascending order of frequency.

Recently, Tyzzer and Weinman (1939) have divided bartonellæ into two genera, *Bartonella* and *Hamobartonella*, both are found in the blood.

but the former produces nodular lesions in animals, whereas the latter remains in the blood and produces anaemia, but not skin lesions

If this applies in the case of bartonella infection of man, another explanation for that each infect more strains of be given, namely, and that one or

**The febrile attack** —The incubation period is usually considered to be about three weeks

There is no dramatic onset but the symptoms develop rapidly with malaise, irregular intermittent fever usually rising to between 100° and 102°F, vomiting hiccough and progressive anaemia. There is headache, pains in the joints and bones, and great tenderness of the bones, particularly those in which there is active marrow, the sternum, ribs, etc., this suggests some association with the observed hyperplasia of the marrow

Most of the other symptoms are the result of the rapidly developing anaemia and need not be detailed here. Hemorrhages into the skin and from mucous membranes and diarrhoea are common terminal symptoms

The course of the disease is very rapid and profound anaemia with red cells as low as 1 000 000 per c mm, may be produced within a week or even less, death usually results in two or three weeks, but may be postponed for several weeks. On the other hand after a week or so the temperature may subside completely, the acute symptoms disappear, rapid regeneration of blood may take place and the patient may recover completely, in such cases the verruga eruptions may or may not follow within a few weeks

**The mild and asymptomatic types** —In the milder type, there are malaise, headaches pains in the bones and joints, possibly gastro-intestinal disturbances, and an intermittent fever. The fever usually subsides a few days before the appearance of the eruptions which may be postponed as long as sixty days

The disease always runs a milder course in children and in them it may be symptomless, it is probably this fact that accounts for the comparative immunity of the local population in endemic areas

Persons with bartonellæ in their peripheral blood may show no symptoms whatsoever. These persons may later develop verruga lesions

**The dermal lesions or verruga peruana** —There are two types of lesion, (i) the military granulo-angiomatous eruption, and (ii) subcutaneous nodule

The 'military' lesions start as small sessile papules, usually on the sites of petechial spots, and increase in size up to that of a split pea, in crops so that later, the lesions cases in which they are at first progressing they

they are p  
legs, and c  
and very  
numerous so that in places they may coalesce



The eruption may last for four or even six months, and a few cases have been reported in which they lasted as long as two years. When they disappear they leave no mark.

The nodular lesions have very much the same consistency as the papules but usually they are softer. They may grow to the size of a pigeon's egg. The commonest sites are on the extensor surfaces of the extremities. The skin is stretched over the nodule, this may be normal in colour, but, if taut, it usually has a pinkish colour.

When this nodule is on or near the knee, or on some other place where it is likely to be damaged, it may ulcerate and form what is known as a 'mular' lesion (apparently for the rather naive reason that mules suffer from a similar lesion), the mular lesion is a nodule with a fungating cap like the crater of a volcano and it is very liable to secondary hæmorrhage.

**Diagnosis**—This presents few difficulties even from a clinical point of view, and is easily confirmed by finding the bartonella infection in the red cells in the febrile stage, or in the reticulo endothelial cells of the dermal lesions. In the latter, parasites are always present, but are not abundant. Escomel (1938) advocates cultural methods as being more certain.

**Treatment**—There is no specific treatment that has any established reputation. An arsenic antimony preparation, Bayer 386B, is apparently effective in the treatment of rats infected with bartonella, in these animals it is given in doses of 0.2 mg per kilo. It is said to have been used with success in 14 cases of the disease in man.

Treatment in the past has mainly been aimed at maintaining the patient's strength, and providing all the necessary materials for blood regeneration. From the nature of the blood picture and from the fact that there is no actual loss of hæmoglobin outside the body, liver extract will obviously be more valuable than iron for this purpose.

**Prevention**—In the absence of exact knowledge of the ætiology no general preventive measures have been adopted in the endemic areas. From a personal point of view, the first important measure of prevention is to avoid spending a night in a known endemic area. If this is not possible then since the disease is almost certainly transmitted by a biting insect protection at night by a sand fly net must be provided.

**Prognosis**—Inhabitants of infected villages seem to acquire an immunity, but probably many die in childhood from the infection.

In foreign visitors to such a village infection appears to be almost certain and the death rate amongst those infected is of the order of 50 per cent.

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# YELLOW FEVER

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## PREVENTION

*Aedes control**Prophylactic inoculation*

History of yellow fever vaccination

*Special measures in India*

## TREATMENT

## PROGNOSIS

**Definition** — Yellow fever is an acute specific fever of varying severity but characteristically one of great intensity and associated with toxic jaundice and albuminuria, it has a limited tropical distribution, and is caused by a filtrable virus which in the urban, either epidemic or endemic form of the disease is transmitted from man to man by *Aedes* mosquitoes and in its jungle form is transmitted from its jungle reservoir to man by other means.

**Introduction** — The importance of yellow fever to India and countries further east lies in the fact that though the disease has up to the present never appeared in these countries the why it should not invade them at some history of this disease shows that it and in the American continent, from which were previously free from it in India the stage is approaching for an explosive epidemic should the virus ever be let loose here. It is therefore essential that we in this country should take every precaution to prevent this catastrophe and if this invasion ever occurs we should be ready to deal promptly with any isolated case that appears, in order that we may stamp out the disease before it gets a firm footing.

In this matter, India has not only herself to consider but she has a special mission in being in the front line in the defence of the rest of Asia. She has not only her thousand million or so to gain an effective would sweep through the rest of tropical Asia, and in these sanitarious backward countries there would be little hope of controlling it until it has run its course and decimated the populations of this and other eastern tropical countries.

Whilst yellow fever is a disease that has from time to time extended its domain it is, on the other hand, one that has been very effectively controlled in many countries where it was firmly established and had become a serious menace to the community. Yellow fever has always been held as an example of how medical research having shown the way, sanitary measures have been brilliantly successful. One time the hope was a triumph over this disease.

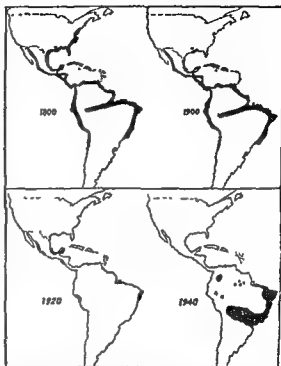
India's problematocal safeguards—It was at one time suggested that there are probably minor differences in the *aedes* mosquitoes of this country, which make them incapable of transmitting yellow fever, this has been shown not to be the case, for *aedes* collected in India have been used in transmission experiments and have been shown to be capable of transmitting the infection

Figure 86 demonstrating three phases in the history of yellow fever in the American continent

Phase 1.—Between 1800 and 1900 the disease almost entirely disappeared from the United States, largely as a result of general sanitary improvement

Phase 2.—The complete disappearance from the United States and the reduction in Central and South America between 1900 and 1920 was due to the application of the knowledge that the mosquito *Aedes aegypti* was the main transmitter, and to measures directed against this insect

Phase 3.—The apparent extension of the disease between 1920 and 1940 is really an extension of our knowledge of the disease, with the discovery of jungle yellow fever



A second hope namely, that dengue or some other similar widespread infection, might have produced immunity to yellow fever in our populations, has also been abandoned after the discovery that of the many hundreds of samples of blood collected in various parts of India, none showed any evidence of immune bodies

We are thus thrown back on the vague hope that as yellow fever has not appeared hitherto, there must be an unknown factor some special local condition, which prevents its gaining a footing

It is not necessary to introduce this 'unknown factor', for the explanation may be that the virus has never arrived in this country, either in an infected individual or in a transmitting mosquito but because this has not happened in the past there is unfortunately no guarantee that it will not happen now or at some future date. This danger is vastly increased by the enhanced speed of transport generally, and particularly by the increase in aerial communications between the yellow-fever areas and the rest of the world. The only safeguard then is increased watchfulness to prevent either an infectious patient or an infected mosquito from arriving in this country. the measures that are in operation to effect this will be described below

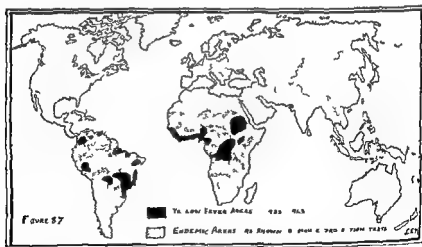
Historical—There is evidence that the disease has existed on the American continent from the time of Columbus; a serious epidemic is reported as early as 1493 in San Domingo. There are many early references to a disease that was undoubtedly yellow fever, from this date onwards, and in the eighteenth century it was so well known that quarantine regulations were introduced in connection with it. It was endemic over a much wider area in earlier days, but it had disappeared from many old endemic areas, even before the exact mode of transmission was known,

presumably as a result of the introduction of general sanitary measures. In America, epidemics were reported as far north as New York and Philadelphia, but during the last fifty years only one epidemic of any importance, the epidemic in New Orleans in 1905, has occurred in the United States. In its eastern sphere, it was at one time apparently rife in Spain, including Gibraltar, in the Canary Islands, and all along the west African coast.

In its history in the West Indies, the disease was almost completely destroyed by the calling at West that landed in the West Indies was almost completely destroyed by yellow fever.

In 1881, Carlos Finlay, a Cuban of Anglo-French parentage, suggested that the disease might be transmitted from man to man by mosquitoes, and carried out experiments to demonstrate this. However, this means of transmission was not generally accepted until, Ross' work on malaria having led to a reconsideration of Finlay's theory, the historical experiments were carried out in 1900 by the American yellow-fever commission consisting of Walter Reed, James Carroll, Jesse Lazear, and Aristide Agramonte. They demonstrated the *aedes* transmission, and further showed that yellow fever was not transmitted by contact or other means. Lazear died of yellow fever, and Carroll developed yellow fever after being bitten by an infected mosquito in an experiment, but recovered. As a result of these observations, control measures were instituted against *aedes* mosquitoes in Central and South America, and by 1920 the incidence of the disease had fallen to a very low point (vide figure 86).

were incriminated as transmitters, with some jungle animals, such as monkeys, as the reservoir of the virus.



#### EPIDEMIOLOGY

**Geographical distribution.**—Yellow fever is now confined almost entirely to the tropics. Most of the endemic areas are on the Atlantic sea-board, though in South and Central America some parts of the Pacific coast are included, and in Africa the endemic areas extend from the west coast for some thousands of miles inland.

In the Americas only one outbreak of urban yellow fever has occurred

from Senegal down to Angola and inland as far east as the Anglo Egyptian Sudan Uganda and Tanganyika and even into Abyssinia An epidemic in the Nuba Mountains in the Sudan which has been recognized as a silent area for some years has recently occurred (*vide infra*)

There are no endemic areas on the east coast of Africa nor anywhere in Asia

**Epidemic features**—From an epidemiological point of view there are two forms of the disease the urban and the jungle The urban form is usually endemic but it may be epidemic especially when new territory is invaded The jungle form is usually sporadic but may also become epidemic

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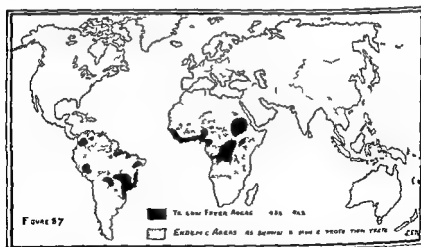
cases of death through an uncertain cause a specimen is taken and examined microscopically (*vide infra*) The mouse protection test is a test to show the presence of protective antibodies in the blood and a positive result indicates that the patient has at some time suffered from yellow fever These two methods have shown the existence of the disease in many parts of South America and Africa where its presence was hitherto not suspected and the findings have usually been confirmed later by the discovery of clinical cases In Africa in certain areas in the Sudan for example many protected individuals have been discovered though the disease has never been reported These have been called **silent areas** and recently in one such area in the Anglo Egyptian Sudan i.e. in the Nuba Mountains near Malakal the silence has been broken by an explosive epidemic In known endemic areas epidemic form for many years children not shown positive protection tests have provided a large percentage

It is

presumably as a result of the introduction of general sanitary measures. In America, epidemics were reported as far north as New York and Philadelphia, but during the last fifty years only one epidemic of any importance, the epidemic in New Orleans in 1905, has occurred in the United States. In its eastern sphere, it was at one time apparently rife in Spain, including Gibraltar, in the Canary Islands, and all along the west African coast. The disease played an important part in naval and military history: in the sixteenth century Drake's fleet was badly infected after calling at West Coast and Spanish ports, and in 1800 a Napoleonic army that landed in the West Indies was almost completely destroyed by yellow fever.

In 1881, Carlos Finlay, a Cuban of Anglo-French parentage, suggested that the disease might be transmitted from man to man by mosquitoes and carried out experiments to demonstrate this. However, this means of transmission was not generally accepted until, Ross' work on malaria having led to a reconsideration of Finlay's theory, the historical experiments were carried out in 1900 by the American yellow-fever commission consisting of Walter Reed, James Carroll, Jesse Lazear, and Aristides Agramonte. They demonstrated the aedes transmission, and further showed that yellow fever was not transmitted by contact or other means. Lazear died of yellow fever, and Carroll developed yellow fever after being bitten by an infected mosquito in an experiment, but recovered. As a result of these observations, control measures were instituted against aedes mosquitoes in Central and South America, and by 1920 the incidence of the disease had been reduced almost to vanishing point (*vide* figure 86).

*Aedes aegypti* was first the only mosquito incriminated, later, other aedes were shown to be potential transmitters, then followed the discovery of 'jungle' yellow fever, with its tremendous implications: jungle mosquitoes, notably *Hamogogus capricornis*, were incriminated as transmitters, with some jungle animal, possibly monkeys, as the reservoir of the virus.



#### EPIDEMIOLOGY

**Geographical distribution**—Yellow fever is now confined almost entirely to the tropics. Most of the endemic areas are on the Atlantic sea-board, though in South and Central America some parts of the Pacific coast are included, and in Africa the endemic areas extend from the west coast for some thousands of miles inland.

ever has occurred  
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from Senegal down to Angola and Egyptian Sudan, Uganda, and Tan-  
epidemic in the Nuba Mountains in the Sudan, which has been recognized  
as a 'silent area' for some years, has recently occurred (*vide infra*)

There are no endemic areas on the east coast of Africa, nor anywhere  
in Asia

**Epidemic features**—From an epidemiological point of view, there are  
two forms of the disease the urban and the jungle. The urban form is  
usually endemic, but it may be epidemic especially when new territory is  
invaded. The jungle form is usually sporadic, but may also become  
epidemic

It is reported that in its original form yellow fever is a disease of  
by jungle  
vns where,  
and then  
endemic

The epidemiology of the disease has recently been studied in two ways,  
by viscerotome surveys, and by the mouse-protection test (*see p 299*)

The viscerotome is an instrument which has been designed for re-  
moving pieces of liver without a full post mortem examination, in all  
cases of death through an uncertain cause, a specimen is taken and  
examined microscopically (*vide infra*). The mouse-protection test is a  
test to show the presence of protective antibodies in the blood, and a  
positive result indicates that the patient has at some time suffered from  
yellow fever. These two methods have shown the existence of the disease  
in many parts of South America and Africa where its presence was hitherto  
not suspected, and the findings have usually been confirmed later by the  
discovery of clinical cases. In Africa, in certain areas in the Sudan for  
example, many 'protected' individuals have been discovered, though the  
disease has never been reported. These have been called 'silent' areas  
and, recently, in one such area in the Anglo-Egyptian Sudan i.e. in the Nuba  
Mountains near Malakal, the 'silence' has been broken by an explosive  
epidemic. In known endemic areas  
epidemic form for many years, chil  
not shown positive protection tests,  
have provided a large percentage  
places distant from the yellow-fever  
been found in the blood of the inhabitants

**Season and altitude**—High temperatures, 75°F and above, and high  
humidity favour the spread  
to coastal areas in the true  
the hot damp months of the  
though it has been reported

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## ÆTIOLOGY

**Historical.**—Many organisms have been isolated from patients and presented as the cause of yellow fever, but the classical mistake of Noguchi is the only one worth recording as Professor Noguchi was a brilliant worker who was led down the wrong path by a clinical mistake—not his own, for he was not a doctor. He isolated a *Leptospira* from cases presented to him as yellow fever, and named it *Leptospira icteroides*. It was in fact *Leptospira ictero-hæmorrhagiae*, the causal organism of Weils disease, which was the disease that these patients were really suffering from. Noguchi died of yellow fever whilst carrying out experiments in West Africa where, dealing now with true yellow fever, he had entirely failed to confirm his earlier findings—a tragic sequel to perhaps the first mistake of a brilliant investigator.

Meanwhile, Adrian Stokes (who later died of yellow fever) Bauer, and Hudson infected Indian monkeys with yellow fever by means of blood filtrates of patients, and thus proved that the disease was caused by a filtrable virus; they further demonstrated that very small quantities of the serum of yellow fever convalescents protected a monkey.

**The virus.**—This is a filtrable virus, of the size of about 18 to 22 micro-microns ( $\mu$ ): it is killed at 60° to 65°C, but survives freezing *in vacuo* for many years. It also withstands the action of some strong disinfectants at 55°C, but is inactivated by the ultraviolet rays in 100,000 living tissues.

**Tropism.**—The virus may be, (i) viscerotropic (or pantropic)—as in the patient with yellow fever or in animals inoculated subcutaneously or intra-viscerally from such a patient, (ii) neurotropic—after serial inoculation in mouse brain, or (iii) atropic, i.e. free from any organotropism—after serial cultivation on nerve-free chorio-allantoic membrane. There is some evidence that the virus may possibly revert to the viscerotropic type, but there is no evidence that it has a neurotropic tendency.

**Susceptible animals.**—The rhesus monkey and the mouse are most susceptible. The common monkey of the Indian subcontinent, but other Asiatic species, are also susceptible, and certain species of yellow fever.

The European hedge-hog also is susceptible to the virus.

**Transmission.**—Infection is very easily acquired in the laboratory, and in contact with the blood of a patient in experimental animals, before the onset of the disease, nearly every member of the staff of a fever laboratory developed yellow fever.

**fever**

The mosquito *Aedes aegypti* is the important transmitter of the urban form of yellow fever from man to man. It is shown to transmit it under laboratory conditions, *vittalis*, *africanus*, and *simpsoni* in Africa, *Hæmagogus capricornatus* in South America, and *Aedes albopictus*.

The mosquito becomes infected if it 'bites' a patient during a period from the appearance of the first symptoms (and probably even earlier, as in the monkey the virus can be demonstrated within 12 hours of inoculation) up to the end of the third possibly the fourth day of the disease, the virus infection develops in the mosquito for some days before the latter becomes infectious, the time varying between four and twenty-eight days according to the temperature at which the mosquito is kept, under natural conditions in the endemic areas, the average latent period is about twelve

sporadically, monkeys have been shown to carry antibodies in their blood

**Factors determining incidence**—The incidence of the disease is conditioned by (a) the number of the vector mosquitoes, (b) the supply of the virus, and (c) the extent of the susceptible material

*Aedes* is a domestic mosquito and thrives best in towns. In the urban form man is the only source of infection, and it is probably mild and unrecognized cases of the disease that are the most important source of the virus. The highest concentrations of (a) the transmitter, (b) the source of infection, and (c) susceptible individuals are found in towns and it is therefore here that the epidemics usually occur

**Immunity**—There is no natural immunity to this infection. Popula-

in earlier life, when the symptoms may be overlooked. The presence of

**Mouse protection test.**—When 4 non-infected mice are taken from each and the serum is mixed with 1.5 ccm of a infected with the neurotropic v intraperitoneally into six mice injection of 0.03 ccm of 2 per

Observe for 10 days if more than three survive the test is positive but if four or more die it is negative that is no immune bodies are present

By diluting the serum further an exact quantitative test is possible which

of blood in the first instance

## PATHOLOGY

**Morbid anatomy**—The typical post-mortem picture includes the olive discoloration of the skin (in the fair-skinned races) and of all the organs and tissues, ecchymoses all over the body, especially at pressure points,

Histological examination of sections of the liver shows characteristic changes that are usually far more extensive than the gross appearance of the organ suggests. The non-necrotic portions of the liver show degeneration. These changes are cloudy swelling, fatty degeneration, and necrosis of the liver parenchyma.

One of the earliest changes is a finely granular appearance of the cytoplasm. The normal yellow-brown color of the liver is lost, and a yellowish-grey color appears.

so that, as the degeneration progresses, large droplets appear. The fatty changes appear to be complementary to the necrosis, being more apparent in the non-necrotic portions of the liver.

The cytoplasm undergoes coagulative necrosis, it may become vacuolated, and hyaline eosin-staining areas appear, chromatolysis occurs in the nuclei. In the non-necrotic portions, there is an increase in the number of red acidophil bodies.

in the central vein  
in which the full range

bodies appear

The extent of the parenchyma involvement will vary from 5 to 95 per cent, in the latter case, only a few areas around the portal sheaths at the periphery of the lobule and around the central vein remain intact, and even these usually show some cloudy swelling under such conditions.

These changes account for the t

In the kidneys there is cloudy swelling, and in some cases hemorrhages into Bowman's capsule and in the cortex, and the tubules are blocked with epithelial debris. These changes readily explain the albuminuria and the eventual anuria.

The spleen shows few macroscopical changes but microscopically there is evidence of endothelial proliferation at the expense of the lymphoid tissue.

to bear the brunt of the attack

The pathology in the jungle form of yellow fever is apparently identical with that of the classical form.

Blood picture and blood chemistry.—There is a leucopenia during the early stages up to the fifth or sixth day, after which there may be a slight leucocytosis. During the first few days there is a lymphopenia which gives place to a granulopenia. Later, there is a relative increase of large mononuclears.

Very early there will be an increase in hæmobilirubinæmia (indirect van den Bergh test positive), and later, when jaundice develops, bili-

## SYMPTOMATOLOGY

**Clinical types**—All degrees of severity will be encountered and division into types is artificial but will perhaps facilitate description

(i) a few hours of attack severity, the presence of albumin in the urine and the slowing of the pulse in convalescence should raise suspicion as to its true nature

During an epidemic, as the Nuba Mountains outbreak, there is often evidence that about 70 per cent of the attacks are apparently sub clinical, but it is probable that, if those natives who showed a positive mouse-protection test could have been observed closely the majority would have shown a mild febrile attack of this kind

(ii) *Incomplete attack*—There is a sharp rise of temperature with

infection, but, in the case of laboratory infection, instances where the

pains all over the body but particularly in the loins and bones, an intense burning sensation and dryness of the skin a furred sharp-pointed tongue with a pink tip and edges a red and swollen face with the eyes bloodshot and 'beady', anorexia and severe prostration

increases, there are hæmorrhages from mucous membranes, into serous cavities, and subcutaneously especially into the scrotum and vulva and at pressure points, and eventually there may be anuria

In fulminant cases the early febrile stage will merge into the toxæmic stages without the characteristic interlude

**Termination**—Death may occur in the febrile stage from hyperpyrexia with delirium or in the 'period of calm' and be associated with profuse hæmorrhages from all mucous membranes, with black vomit, mæna and hæmaturia the patient passing into a comatose state Death seldom occurs

before the third day or after the eleventh, and if the temperature is down by the seventh day the prognosis is good

**The fever**—The temperature rises sharply, reaching 103°F or higher in 24 hours and remains high for three or four days, it then falls usually rather rapidly and may become sub normal for 24 hours—the 'period of calm', but it may rise again to 101° or 102°F for another two or three days or more (see charts, figure 88)

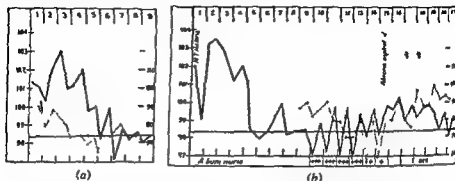


Figure 88 Two yellow fever temperature and pulse charts

(a) A relatively mild case

(b) A case complicated with malaria and abscess formation (Kirk et al 1941)

**The pulse**—This is rapid full and bounding at first, but the pulse rate tends to lower as the fever subsides. The pulse rate is an important indicator of the severity of the disease. The pulse rate is an important indicator of the severity of the disease.

**Jaundice** appears on the third or fourth day and is progressive—up to a dark brown colour in severe cases. Its earlier appearance suggests a bad prognosis. It is a common but not a constant sign and even in moderately severe cases it may not be prominent. It is naturally associated in severe cases with bile in the urine and a bi phasic van den Bergh reaction. Petechial hæmorrhages may appear, and a characteristic erythema of the scrotum or vulva is common. In severe cases large purpuric patches appear.

**Other symptoms**—Insomnia and restlessness are constant but delirium is rare except as a terminal condition. Vomiting may occur with the onset of the fever, as with any high fever, but the characteristic severe vomiting occurs from the third day onwards and may assume a coffee-ground character, the typical 'black vomit' of yellow fever, which always portends a grave issue.

### DIAGNOSIS

**A The clinical diagnosis**—The clinical diagnosis of a typical case presents little difficulty. The sequence of events is very characteristic, there

until anuria supervenes, ...

Even if jaundice is slight during the course of the disease, it will in every fatal case be marked at the time of death.

During the presence of a recognized outbreak, the occurrence of mild fever of two or three days' duration associated with a disproportionate degree of headache and the presence of albuminuria will lead to a suspicion

of yellow fever. In an isolated case of the mild type, it will be almost impossible to make a clinical diagnosis.

**B Laboratory diagnosis** Tests for the presence of yellow-fever

VIRUS INJECTIONS ALSO COULD  
ould be controlled by pro-  
serum. Blood taken for  
the ice-chest, more than a

less certain

**Tests for the presence of immune bodies**—When, in the later stages of

so that mosquitoes are not usually infected after the third day of the disease, for purposes of the mouse protection test the antibodies are seldom present in sufficient quantity to ensure a positive result before about the twenty-first day, the diagnostic value of this test is thus limited. (For technique see p. 299.)

fever

**C Post-mortem diagnosis**—The characteristic changes in the liver enable a post-mortem diagnosis to be made by naked-eye and histological examination.

Portions of the liver can be taken for the purpose by carrying out a full post-mortem examination or, when this is not permitted, by removing a piece by means of the viscerotome, the instrument devised for removing small portions of tissue for histological examination.

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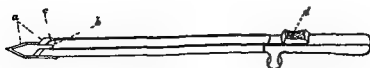


Figure 89 The viscerotome

- a Cutting edges for introducing viscerotome
- b Sliding guillotine blade
- c Groove for sliding guillotine blade
- d Thumb grip for closing the sliding guillotine blade

a solid organ, the three fixed blades make a deep U-shaped incision, the flexible blade is moved forward, completes the open side of the U to make a more-or-less square incision and then, dipping downwards behind the rectangular block of tissue to meet the lower blade, it severs a piece from the rest of the organ and encloses it in the viscerotome, the instrument is then withdrawn, opened, and the contained piece of organ removed.

**Technique**—The entry point of choice is in the epigastrium just below the ensiform cartilage and close to the costal margin on the right side. The direction of the thrust is at an angle of about 10° with the horizontal and about 20° with the body surfaces from left to right (figure 90). The instrument which must be closed (figure 91a) is pushed through the skin and the abdominal wall with a sharp thrust. When the lower fixed blade has penetrated the liver the flexible blade is opened about an inch, the instrument is thrust further into the organ for about half an inch and then the flexible blade is pushed forward again and held firmly in this position while the viscerotome is withdrawn from the body.

The flexible blade is withdrawn and the piece of liver removed and placed in solution for subsequent sectioning.

The hole made by the instrument is now plugged with cotton wool to prevent oozing and the skin wound is sewn up if this is considered necessary. The warning may seem superfluous but it must be emphasized that this viscerotomy is only a *post mortem* procedure.

**Differential diagnosis**—The most constant and prominent symptoms of yellow fever are fever and jaundice, therefore the diseases with which it is most likely to be confused are severe malaria of the 'bilious remittent' type, blackwater fever, Weil's disease, infective hepatitis, and catarrhal jaundice. Certain fatal liver conditions such as acute yellow atrophy and carbon tetrachloride poisoning might be mistaken for yellow fever in the latter the hepatic necrosis is central. The milder forms of yellow fever might be confused with relapsing fever, dengue, or influenza.

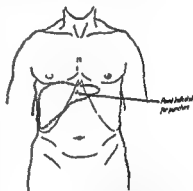


Figure 90 Showing point of entry and direction of thrust of the viscerotome



Figure 91 Viscerotome (a) shut and (b) open

In the malarial fevers the parasite (a) should be easy to demonstrate, while the jaundice appears earlier and tends to improve, in blackwater fever parasites may not be found but the hæmoglobinuria of this condition should not be mistaken for the hæmaturia of yellow fever. Similarly, in relapsing fever the spirochæte is usually found in the peripheral blood. The saddle back temperature of dengue is not unlike that of

yellow fever but the dengue rash when present is characteristic, and jaundice does not occur.

The only real difficulty that is likely to arise is in differentiating Weil's disease, and in this case we have the precedent of Noguchi's classical mistake (For the exclusion of Weil's disease see p. 251).

**Precautions**—If there seems to be a serious possibility that the case is yellow fever, the utmost precautions must be taken immediately and the patient kept rigidly under a mosquito net day and night. Also it should be remembered that the virus is present in the patient's blood and is

unneutralized by antibodies for at least three and in some cases up to four days, and that therefore every care should be taken to prevent his blood touching anyone's unprotected skin during the process of blood withdrawal (In most countries immediate notification to the health authorities is imperative)

### PREVENTION

For the disease to be spread, there are three requirements—the virus, the transmitting mosquito, and the susceptible population

The main successes in yellow fever prevention in the endemic areas have been achieved by aedes control. Aedes is a mosquito which is very local in its habits, it bites during the day, so that thorough spraying of

population, very careful inspection at frequent but irregular intervals is essential. It has been found that, provided the aedes index is reported below 2 per cent (that is, only 2 per cent of houses inspected show aedes breeding places), yellow fever will not spread.

Aedes seldom flies more than a few hundred yards from its breeding place, and therefore control for an area of four hundred yards around a house, or aerodrome, is usually considered sufficient. Similarly, if ships are moored a quarter of a mile from the shore in a yellow-fever port, they are considered to be safe, but this does not take into account the danger of mosquitoes being brought from the shore in small visiting craft, or in coal or other lighters.

It is beyond the scope of this book to describe in any detail the procedures that should be adopted against these mosquitoes, but besides the elimination of breeding places and other anti-larval measures and the destruction of the adult mosquitoes by spraying (*vide* p 115), for personal protection some deterrent application should be smeared on the ankles, wrists, neck and other exposed parts of the body. For this purpose the following makes an effective cream (*see also* p 119) —

Citronella oil	8 parts	Soft paraffin	57 parts
Camphor	1 part	Hard paraffin	29 parts
Liquid extract of pyrethrum	5 parts		
			100 parts

Another measure that is now being adopted with increasing frequency in several countries is the reduction of the susceptibility of the population at risk by prophylactic inoculation.

History of yellow fever vaccination —Hindle in 1928 suggested prophylactic inoculation, and Sawyer *et al* (1931) introduced sero-vaccination which consisted in giving an emulsion of the liver of an infected monkey in combination with convalescent serum, the latter prevented the development of the disease, but

been carried out

The vaccine is made from a strain which was originally a virulent pantropic virus that had been passaged some hundreds of times on mouse-embryo tissue-culture medium until it completely lost its viscerotropic



qualities and became a neurotropic virus. then it was passaged again some hundreds of times, on chick embryo from which the brain and spinal cord had been removed, so that it lost its neurotropic qualities. The first virus thus made caused no serious trouble, but an appreciable percentage of those inoculated suffered from jaundice, this was possibly due to an accidental contamination with some other virus. The present strain is entirely innocuous, the injection is not followed by any local or general reaction\*, only one injection of 0.5 c.c. (1,500 mouse-protection units) is necessary, and it produces an immunity which is protective from the first day and lasts for a considerable time—there is some diminution in the protective power of the blood at the end of four years, and revaccination is recommended after this interval.

All persons dealing with yellow-fever patients or infected animals, their blood or excreta, or the preparation of vaccines, should be inoculated. In South America and Africa, especially in areas where there is no other measure of control, this should be used in these circumstances.

**Special measures in India.**—In this country, the susceptible population is very large, and the disease is relatively uncontrollable. The third direction for consideration must be

Towards this end a very great deal is being done. Air traffic has introduced a new source of danger and it is on this that most attention is now being centred, though other possible channels of entry, e.g. via Bombay and other west coast sea-ports where for many years precautionary measures have been in force, are not being forgotten.

We must first return to Africa. The planes from Lagos on the West Coast, after passing through active yellow-fever areas, join the Cape-to-Cairo route at Khartoum. There is a considerable amount of air traffic from Lagos to Khartoum and thence to Cairo. It is thus obvious that a person could get on board a plane at Lagos in the early stages of the incubation period of yellow fever, change at Khartoum, again at Cairo where he could pick up the regular service plane from Europe to India and reach Karachi even before symptoms had developed. Further, Malakal, an aerodrome in the Anglo-Egyptian Sudan on the Cape-to-Cairo route, has long been recognized as a 'silent' yellow-fever area, for a large percentage of the population have antibodies in their blood, as shown by the mouse-protection test, and from time to time suspicious cases have been reported. Such 'silent' areas are potential dangers, and from them an infected person might arrive in India at an even earlier stage. It was therefore laid down by the International Sanitary Convention for Aerial Navigation that, for purposes of this convention, 'silent areas' shall be treated as yellow-fever areas.

from all necessary precautions whenever a passenger is allowed to come to

\* Recently, an infective hepatitis has recurred amongst USA troops that had received prophylactic injections from certain batches of yellow fever vaccine. The first symptoms appeared between 40 and 100 days after vaccination and the resultant invalidism averaged two months. Official figures are naturally not yet available but many thousands of soldiers were affected, two per thousand of hospitalization, but a contaminating virus that caused the infection of the infected batches and the accident is not likely to recur.

Karachi from the endemic or 'silent' areas unless they have passed through either Khartoum or Cairo, which are anti-amaryl aerodromes [that is to say, especially equipped for anti-amaryl (anti-yellow-fever) measures, which include local control of aedes mosquitoes and 'disinsectization' of the aeroplanes before they leave], and unless they carry a certificate of disinsectization from a competent authority in one of these two places. For disinsectization 'pyroside 20', a pyrethrum spray with a kerosene base, has been used, but there are similar preparations with watery bases which are safer and almost, if not quite, as effective (see p 116).

In India, the further precautions that are taken include the following:—

(c) Inside of the plane is carried out before is removed  
 a 'disinsectization' certificate, it will be all persons on board other than those who have been protected against the disease by a previous attack or by satisfactory inoculation, will be subjected to isolation for a period not exceeding nine days from the time of arrival of the aircraft.

(n) in India and not more than two years before his departure from the yellow fever-infected area

(d) Finally, aircraft are prohibited from entering India from the west except at Karachi where the organization for carrying out these measures exists

The sanitary authorities in India have had a great fight with the international authorities to get these measures enforced in other countries, but they insisted on certain minimum requirements, which were eventually

to the present, has depended

It should perhaps be repeated that in no circumstances is one permitted to import yellow-fever virus into India, for any purpose whatsoever

*Aedes aegypti* also transmits dengue, and the rapidity with which this infection spreads gives one some idea of how yellow fever would spread if it once gained a footing in India. Special measures are taken at aerodromes and in dock areas to control this species, as an extra precaution against yellow fever. In the event of an invasion by yellow fever, aedes control would have to be given priority over all other sanitary measures throughout the whole country

ding some coming  
 oleale inoculation  
 vaccine are being

## TREATMENT

There is at present no recognized specific for this disease, so that the treatment is essentially symptomatic. The extreme variability in the

severity of the disease accounts for the innumerable specifics that have gained local reputations

The patient must be kept in a mosquito-proof room or under a net

and consist mainly of milk-water, albumin water and barley water. The use of alkaline fluid should be given, sodium citrate or bicarbonate, by mouth if possible, otherwise per rectum. Glucose should also be given liberally by mouth. A 2 per cent solution together with insulin may be given to reduce hypoglycaemia. To reduce gastro-intestinal acidity is looked upon by some workers as a specific —

R Liquor hydrargyri perchloridi  
Sodii bicarbonatis  
Aquam

min ii  
gr vi  
ad 3i

Take hourly

in doses of calomel half-hourly. Vomiting should be avoided. Severe stomatitis and parotitis may occur.

hydr

Other treatment is symptomatic —

**Vomiting** — Ten minims of adrenaline (1 in 1,000) by mouth or  $\frac{1}{4}$  grain of cocaine in an ounce of water

**Black vomit** — *Liquor ferri perchloridi*, Mx, to be repeated

**Hyperpyrexia** — This should be treated by hydrotherapy rather than antipyretic drugs

**Restlessness** — Phenobarbitone, gr 1 to 3 by mouth or gr 1 intramuscularly

**Anuria** — Dry cupping to loin, warm colon wash and warm citrate saline bladder wash, in addition to glucose and sodium bicarbonate intravenously

Stimulants may be required in the later stages, especially during the 'period of calm' when collapse is not infrequent

Convalescents should be treated cautiously, especially with reference to diet which should be increased very slowly, indiscretion may have serious consequences

### PROGNOSIS

The disease was at one time considered to be nearly 100 per cent fatal, but later it was realized that, in indigenous populations in particular, the infection often leads to a milder attack and that even Europeans in Africa often escape the disease. It should be recognized that in most endemic areas, a large proportion of the population is suffering from the disease.

In most endemic areas, a definite clinical attack of the disease will vary considerably according to circumstances, but in semi-immune populations it is undoubtedly sometimes a very mild disease, comparable to dengue both in its severity and in its clinical manifestations. In the recent epidemic in the Anglo-Egyptian Sudan, the mortality is reported to have been 10 per cent

It is however, an alarming disease when it occurs in epidemic form and their utter helplessness to assist in any way the patient with a severe attack leaves a lasting and horrifying impression on the mind of physician who have been through an epidemic

\* Recent work has shown the liver protecting value of a high protein diet with choline. It seems possible that the parenteral administration of the amino-acids cystine and methionine might be even more advantageous than glucose in this disease

**Addendum**—No outstanding observations have been made during the last two years but the recent work on the reservoir of infection of jungle yellow fever has clarified the position (Bugher *et al.*, 1944)

where a continuous supply of fresh fuel was maintained. In the jungle this is supplied by migrating mammals and marsupials as well as by the newly born and it has been shown that jungle foci of infection tend to move from place to place.

The infected jungle mosquitoes will survive for several months so that they are more truly the reservoirs of infection. They may also migrate into coffee plantations where they come into closer contact with man and may become the vectors in a small localized epidemic. The greater danger is that a man who is sporadically infected in the jungle as frequently happens when tall jungle trees are cut down and the tree top dwelling *Hæmagogus capricornis* swarm around the woodmen will go into a town during the incubation period and start an *Aedes* born epidemic.

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# RIFT VALLEY FEVER

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**Definition** — Rift valley fever is an epizootic hepatitis with a limited geographical distribution in certain circumstances it is transmitted to man in whom it causes a mild febrile disease

**Discussion** — The importance of this disease lies on the fact that it may be mistaken for mild yellow fever, because of its African distribution and because of the hepatitis. It is caused by a specific filtrable virus, of which examples that have not yet achieved

**Historical** — Though a very similar disease was encountered in this locality in 1931, the disease as now known was described

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**Epidemiology** — The disease is so far confined to the Rift valley in Kenya and to those coming in contact with the infected cattle or sheep or with the virus in the laboratory

**Ætiology** — The disease is caused by a filtrable virus 23 to 35  $\mu$  in size which is found in the plasma and is attached to the red cells it is present for six days after the onset of the attack after which it is neutralized by antibodies that appear in the blood. The virus has an affinity for the nervous system. It does not appear in the urine

It is transmitted through the mucous membranes or the scarified skin. Mosquitoes of the genus *Mansonia* especially *Mansonia fuscipennata*, are suspected as carriers of the infection in nature.

**Immunity**—There is immunity after an attack, which lasts for some years, certainly six but is probably not permanent. In animals it lasts only about six months.

**Pathology**—The morbid anatomy has been studied in animals. The most characteristic feature is the congestion of the liver, but eventually the cytoplasm of the liver cells becomes vacuolated.

**Blood picture**—In the early stages of the attack and this is the case in man and animals, the lymphocytes are increased.

**Symptomatology**—The incubation period is from four to six days. The onset is sudden, with rigors (often), malaise, nausea, headache and photophobia, backache, and a feeling of fullness in the liver region. The

1

during convalescence.

**Diagnosis**—A diagnosis can be made by inoculating the blood during the first few days into mice. 0.1 ccm being given intraperitoneally, the mouse will develop an encephalitis in 48 to 72 hours. As many other viruses kill mice the identity of the agent must be ascertained by neutralization tests.

A retrospective diagnosis can be made by the mouse protection test (cf. YELLOW FEVER) or by a complement deviation test which remains positive for at least six months.

The disease has to be differentiated from influenza, dengue, sand fly fever, other forms of hepatitis and mild yellow fever.

**Prevention**—A vaccine made from a fixed neurotropic virus has been used with success in prophylaxis in sheep.

**Treatment**—No specific treatment for the condition has yet been discovered. The symptomatic treatment consists in giving glucose freely by mouth and intravenously. Convalescent serum is reputed to cut short an attack.

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# DENGUE SAND-FLY GROUP

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**Introduction**—The two main clinical syndromes of this group are the mosquito borne dengue and the sand-fly-borne sand-fly fever. Both diseases are caused by filtrable viruses, are clinically characterized by short fever, a rash, severe pains in the joints and back, and headache and are diseases of very low mortality. Megaw, who was one of the first workers to insist on the recognition of this group as a group—a procedure which

Most workers however, who have had experience of both diseases, recognize the clear differences in the syndromes, and consider the two as quite separate diseases probably caused by two distinct viruses. Admittedly, it may be very difficult in any one particular case to be dogmatic and say this is definitely a case of sand fly fever or of dengue but given half a-dozen cases of each disease it will usually be possible to say, quite definitely, which set is dengue and which sand fly fever. Further, there is no evidence of the existence of any cross immunity.

Megaw postulates a third member of this group—dengue of unknown vector. Our knowledge of the short fevers of the tropics is certainly far from complete and a possible example of another disease of this group is so called—  
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 by a tick  
 at 1940)

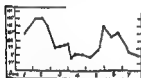


Figure 92 Temperature chart of Colorado tick fever (Topping et al 1940)

The dengue-like nature of this disease (vide figure 92) seems to be more certain than its suggested mode of transmission. We must realize that the future may add more members to this group,

purpose and might imply the recognition of a single specific clinical syndrome whose full aetiology was unknown

## DENGUE

**Definition**—Dengue is a short febrile disease of about 7 days' duration, characterized by severe pains all over the body, rashes, and a terminal rise of temperature. It occurs endemically and epidemically in the coastal areas of many tropical and sub-tropical countries. It is caused by a filtrable virus, and is transmitted from man to man by *stegomyia* (aedes) mosquitoes.

**Historical**—Dengue has been recognized in various countries as a distinct

sufferer

In 1903 Graham transmitted the disease by the agency of mosquitoes which he had had as a fever in 1902 and Craig transmitted dengue in blood

They experimented with culex and In 1916 Cleland Bradley and McDonald

described a few years later Siler Hall and

these observations and demonstrated the whole transmission cycle (vide *infra*)



## EPIDEMIOLOGY

**Geographical distribution**—It has a wide, tropical and sub tropical distribution in the four major continents, and it occurs in Queensland in Australia. In America except for a few isolated epidemics, eg the extends from Charleston in South

distribution of aedes, and it is therefore confined mainly to coastal areas

**Epidemic features**—It is a disease of towns rather than country areas. It does not occur at an altitude of more than 6,000 feet and it is confined to the plains in the sub-tropical regions. In the tropics, it is endemic but subject to cyclical and seasonal exacerbations, in the sub tropical and temperate zones it is usually epidemic (eg the epidemics in Dallas in 1897 and in Athens in 1927 when at least half the inhabitants suffered and the public services were temporarily dislocated)

**Seasonal incidence**—In the sub-tropics, it is a late summer and autumn disease. In the tropics it is variable and again dependent on aedes activity in many places, it is perennial, but it tends to show a monsoon rise and in Calcutta the highest incidence is in August and September

**Age sex and race**—All ages and both sexes are

inhabitants nearly always enjoy some if not complete immunity through previous infection it is always the visitors who are attacked. Every year we have half a dozen or more cases amongst our post graduate students, and the patients are always the visitors to Bengal though such students represent only a small percentage of the class

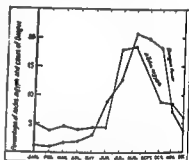


Figure III Seasonal curves of aedes and dengue in Calcutta

## ÆTIOLOGY

**The virus**—The virus passes through  $L_1$  and  $L_2$  Chamberland filter for the first three days of the incubation period. It is destroyed by heat and by the action of antibodies.

**Transmission**—*Aedes aegypti* (previously known as *Stegomyia*) is the vector. The virus undergoes development in the mosquito, which is capable of transmitting after the 8th day and remains infectious for the rest of its life. *Aedes* alone transmits, not *Culex*. In the Philippines *Aedes albopictus* is the transmitter.

**Immunity**—An attack causes a certain amount of immunity, but not complete immunity. The first attack is usually a bad one, the second is a mild one, and the subsequent ones are usually abortive amounting to little more than a feeling of malaise for 24 hours or less and possibly being unnoticed. Recent work shows that there is no cross immunity with sand-fly fever or yellow fever.

## PATHOLOGY

Dengue is not a fatal disease, so that little is known about the morbid anatomy.

The blood picture has certain characteristic features, there is marked leucopenia, which is a granulopenia. The Arneth count shows a marked

shift to the left. There may be a distinct leucocytosis following the attack, with the Arneth count still maintaining its leftward shift.

There is nothing characteristic in the urine, it is highly coloured and there is usually a trace of albumin.

### SYMPTOMATOLOGY

The incubation period is usually 4 to 7 days. In extreme cases it may be from 2 to 15 days.

The onset is sudden, the temperature rising rapidly to 103°F. Although the temperature is very high, there is seldom a typical rigor. There is severe headache and pains in the eyeballs with marked photophobia, pain in the back, in the bones, and all over the body, causing the patient to assume a characteristic stiff gait when walking and to toss from side to side in his bed. The tongue is furred and red at the tip. The face is flushed and the eyes are suffused. There is very often general glandular enlargement.

Other symptoms include constipation or a 'critical' diarrhoea accompanying the second rise of temperature.

The fever varies considerably from case to case and from epidemic to epidemic, but there is a tendency for one type to predominate in each epidemic or seasonal exacerbation. The seven days temperature is the classical form. The temperature remains high for two or three days, coming down slowly to about 99°, and then rises suddenly on the 6th or 7th day and drops to normal again.

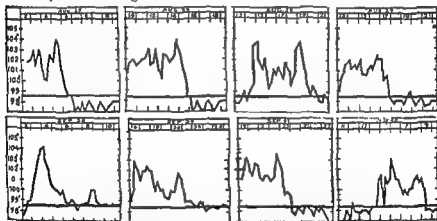


Figure 94 Showing temperature charts of six consecutive cases of dengue and two additional charts the last being a hospital infection

Two cases -- 2 cases -- 2 cases

a high remittent character

Sometimes there is quite a high temperature before the final rise

the two phase type of temperature chart

In milder epidemics there is only a single rise of temperature, a sharp rise for two days which then fades away. In this one phase or abortive type the second rise of temperature may be so slight that it is not noticed, or it may not occur at all.

In exceptional cases, the second rise is higher than the first. It is a three phase temperature.

The pulse is usually very low indeed, down to 40 per minute.

**Rashes**—There are two at the onset, a transient and chest, and the second even after the fall of temperature on the 7th or 8th day. The latter is a macular or scarlatiniform rash, usually commencing on the hands and wrists or legs and extending to the chest, not usually to the face but otherwise all over the body. It may be very irritating and in severe cases there is later marked desquamation.

The diarrhoea is not common. They include acute depression amounting to definite melancholia, multiple joint pains, pain in one or two joints which may be very troublesome and last for two or three months or even longer, and a tendency to faint.

**Variations in the symptomatology**—The different temperature charts that are encountered are discussed above, other symptoms especially the rashes, show the same characteristics. The rash is epidermic and in 10 per cent of cases it never occurs.

### DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis must be made on the clinical evidence and by a process of exclusion, there are no positive laboratory tests. The short fevers that have to be excluded include sand fly fever (*vide infra*), malaria—definite rigor, periodicity, and the finding of parasites, influenza—catarrhal symptoms and absence of rash, measles—catarrhal spots, scarlet fever—not common in absence of rash and finding of the (leptospiral). The more serious conditions of greater intensity with much albuminuria, small pox, and typhus.

The severe pains might simulate rheumatic fever, and the rash, which is sometimes very intense, secondary syphilis.

### PREVENTION

The only practical measure of dengue prevention is the control of *Aedes*. *Aedes* have a very limited flight, so that the elimination of their breeding places does not present very great difficulties if properly organized. Spray-killing of the adult mosquito should also be undertaken, in both day and night quarters. Other measures should include screening and/or the use of mosquito nets, and the application of repellent substances to the ankles, wrists and other exposed parts of the body (*vide supra*, pp 119 and 305).

### TREATMENT

There is no specific treatment.

A salicylate mixture should be prescribed and a brisk purgative, for example,  $\frac{1}{4}$ -grain doses of calomel every half hour up to six doses followed by salts in the morning. Aspirin may be given in addition for the pains, and bromides or phenobarbitone for the sleeplessness. For persisting joint pains local analgesic ointments or liniments, such as oil of wintergreen, should be applied, and a mixture containing tincture of belladonna and tincture of colchicum given.

**Prognosis**—This is always good. In extensive epidemics, the death rate has been placed at about 0.2 per cent, the deaths occurring amongst old and debilitated persons.

# SAND-FLY FEVER

**Definition**—Sand-fly or phlebotomus fever is a fever of short duration characterized by headache, pain in the eyeballs and all over the body, and often by great prostration. It is caused by a filtrable virus which is transmitted from man to man by sand-flies.

particularly in India. It is a UO), climatic fever, and separate entity. In 1909 blood infection and that the virus was filtrable and Birt showed that sand-fly fever and others (1934) of the fever.

# EPIDEMIOLOGY

It has a wide geographical distribution in tropical and sub-tropical regions, but mainly in the latter, it occurs in the Mediterranean littoral including north Africa, Egypt and Palestine, in Syria, Iraq, Iran, north-west India, and central and south America.

It does not usually occur above 4,000 feet, and never above 7,000 feet.

It usually occurs in late summer and autumn (vide figure 95), but the incidence curve will vary in different localities. The sand-fly season in north-west India starts in April or May and lasts until October.

# ÆTIOLOGY

**The virus**—The virus is filtrable and passes through L<sub>1</sub> and L<sub>2</sub> Chamberland filters. It circulates in the blood one day before and during the first two days of the attack.

Monkeys can be infected.

**Transmission**—It is transmitted by *Phlebotomus papatasi*, the golden-coloured sand-fly. The virus undergoes a stage of development in the sand-fly, during which it is not transmissible. Transmission will occur on the seventh day after the infecting feed, and the sand-fly remains infectious for the rest of its life. The virus is said to be transmitted to the next generation, possibly the larvae become infected by feeding on the bodies of dead adults.

Transmission is a generally accepted fact that virus is transmitted to L<sub>1</sub> and L<sub>2</sub> filters.

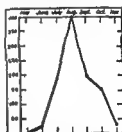


Figure 95 Seasonal distribution of sand fly fever in Palestine (Walker and Dods 1941)

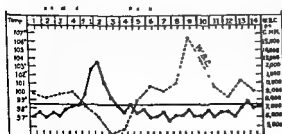


Figure 96 Temperature chart with leucocyte count records in sand-fly fever (Whittingham, 1938)

change is an increase in the permeability of the blood tissue barrier especially of the blood-brain barrier, though apparently the virus does not pass the latter.

The blood picture shows a sharp leucopenia associated with an absolute increase in immature granulocytes during the fever, often followed by a leucocytosis (see figure 96).

## SYMPTOMATOLOGY

The incubation period is from 4 to 10 days, usually about 6 days. The onset occurs with chill. The average duration of the fever is 3 to 4 days, but it may be longer. A secondary rise is comparatively rare. The pulse is strikingly slow, often from the second day of the fever.

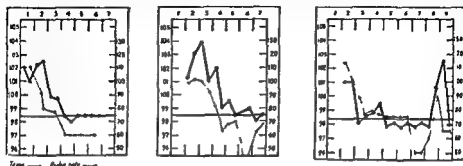


Figure 97 Three sand fly fever temperature charts, the first two are typical, and the last is unusual and shows a terminal rise suggestive of dengue (Walker and Dods loc cit)

There is a general puffiness, and uniform flushing of the face, the con-  
prostra-  
ained by  
late, but  
much the  
pain on  
There  
round

There may be general hyperæsthesia of the skin of the face, head and trunk, and absence of the biceps and supinator reflexes.

Papilloedema has recently been reported as constantly present in this disease in a severe epidemic in British soldiers (Shee, 1942).

**Complications**—There are not very many complications, but a condition suggesting benign lymphocytic meningitis has been reported.

**Diagnosis and differential diagnosis**—This is clinical and by a process of exclusion. The disease has to be distinguished mainly from malaria, dengue and influenza, the complete absence of catarrhal symptoms helps in the last named. The author has seen a case diagnosed as small-pox, the

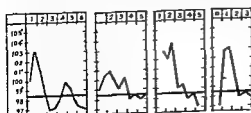


Figure 98 Sand fly fever temperature charts from Peshawar (Anderson 1941)

sand fly bites on the forehead and wrists providing the characteristic shotty feeling.

The muscular pains and more especially the band-like pain around the lower part of the thoracic cage suggest Bornholm disease. Sand fly fever can be distinguished from benign lymphocytic meningitis, which it may simulate, by the low lymphocyte count in the cerebrospinal fluid in the former.

## PREVENTION

Preventive measures are all aimed at the sand-fly. They can be summarized as follows —

- (a) The avoidance of localities that are heavily infested with sand flies or from the nature of the terrain likely to be so infested at the favourable season
- (b) The elimination or treatment of their breeding places
- (c) The elimination or treatment of the resting places of the adult fly
- (d) Personal preventive measures against the bites of sand-flies

(a) Much can be done by the proper choice of a camping ground especially by the avoidance of a 'cool' river bank, moving a bed or tent even a hundred yards may make all the difference. Top floors are preferable to ground floors, and open airy rooms to shut-in ones.

(b) The sand-fly requires, for its breeding place, darkness and protection from air currents, a comparatively even 'effective' temperature, moisture which also helps to maintain this temperature, and food in the vegetable matter

that it is only necessary to control the round the house or camp, a provisional apted for this. They breed in heaps of uted buildings in the banks of rivers, streams, or ditches, in the internal or external cracks in any form of building, in disused fireplaces and chimneys, and even in the cracks in the dried earth.

Inhabited buildings should therefore be kept in repair and all cracks filled up before the sand-fly season. Where this is not possible for any reason, they can be treated with a mixture consisting of 10 per cent of naphthalene dissolved in kero-sene—four pounds of naphthalene balls added to a 4 gallon drum of kerosene and allowed to dissolve for three days.

(c) Resting places for the adult flies should be reduced to a minimum by removal of curtains, pictures, superfluous furniture, and collections of clothes, and the elimination of all dark corners. Rooms should be fumigated or sprayed with any suitable anti-malarial fumigant or spray. The fumigation. Closed drains

sufficiently fine mesh to keep out sand-flies—for this purpose the nets must be 45/46 mesh (*vide p 119*), or electric fans where these are available, the wearing of suitable protective clothing in the evenings, protection of the ankles by means of mosquito boots, and the application of repellent creams to the ankles and exposed parts of the body (*vide pp 118 and 119*).

**Treatment.**—This is mainly symptomatic. Aspirin, phenacetin and caffeine, or phenobarbitone in more severe cases, should be given for the pains and headaches. Dover's powder is useful, and Manson-Bahr considers that opium is a specific, recommending doses of 30 minims of the tincture.

Prognosis is uniformly good.

## COMPARABLE FEATURES OF DENGUE AND SAND FLY FEVER

**Common**—They are short fevers with many common clinical features, are caused by filtrable viruses, and are transmitted by insects. The virus is present in the patient's blood for 3 days and takes about a week to develop in the insect.

**Distinguishing**—These can be best shown in the form of a tabular statement:—

## SYMPTOMATOLOGY

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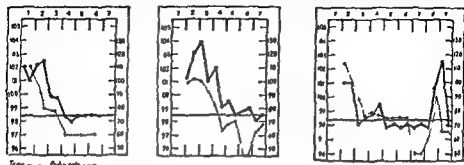


Figure 97 Three sand fly fever temperature charts the first two are typical, and the last is unusual and shows a terminal rise suggestive of dengue (Walker and Dods loc cit)

There is a general feeling of malaise and a sense of the con-

the fauces are congested. The late but the game as in dengue, but headache and pain on movement of the eyeballs. There is in some epidemics a sensation of an intense band-like restriction round the liver region, which suggests hepatitis, or severe hepatic congestion.

A rash is exceptional.

There may be general hyperæsthesia of the skin of the face, head and trunk, and absence of the biceps and supinator reflexes.

Papilloedema has recently been reported as constantly present in this disease in a severe epidemic in British soldiers (Shee 1942).

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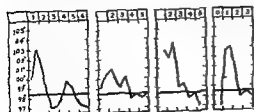


Figure 98 Sand fly fever temperature charts from Peshawar (Anderson 1941)

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## Dengue

## Sand-fly fever

1	Virus present for first 3 days of fever	Virus present day before fever and for the first 2 days after onset
2	Transmitted by <i>Aedes aegypti</i>	Transmitted by <i>Phlebotomus papatasi</i>
3	Eight days' development in mosquito	Seven days' development in sand fly
4	Mainly tropical	Mainly sub-tropical
5	Fever lasts 5 to 7 days usually, sometimes less	Fever lasts 3 to 4 days usually, sometimes longer
	Secondary rise of temperature occurs in 25 to 80 per cent of cases in different epidemics	Rare
6	Primary rash occasionally, secondary rash all over the body, in most epidemics	Rare
7	Immunity is variable and tends to be short	Immunity is usually complete

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Addendum.—Several outbreaks of short fever of unknown aetiology have been

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appeared and the disease disappeared

Plague was described by various writers in the classical period as occurring in the countries around the eastern Mediterranean. The Justinian pandemic of 543 A.D. is said to have reached Europe from Egypt and spread throughout the Roman Empire along the lines of human communication. The greatest European epidemic however, was the Black Death starting in 1346 A.D. It is reported to have reached Europe from the near east; it spread all over Europe and

adjacent countries, and killed, we are told, one-quarter of the population of the then-known world. References to this great outbreak occur in the histories of many countries. Another European epidemic occurred in the ten years following 1664 and in London about one-sixth of the population is said to have died in the first two years. There were only the great visitations of plague, and actually plague was never absent from Europe between the 14th century and the beginning of the 19th century, in the years between the great pestilences many minor outbreaks occurred.

The third great pandemic of the present millennium started in 1894 and is now apparently drawing to its close. It originated in Yunnan province in China and rapidly spread to Hong-Kong, Japan and the Philippine Islands. In 1896 it appeared in Bombay which had been free from plague for nearly two hundred years and thence it spread over most of India. From India it spread to Africa and to Australasia (1899), Hawaii Central and South America (1899), to the United States (San Francisco, 1900), and to a limited extent to Europe. This pandemic involved almost the whole world, India, however, suffered most. In some of the early years of this century the deaths from plague in India numbered over a million, and in 1907 they reached a peak of nearly 14 millions, since when they have steadily declined.

In the United States, on the other hand, from the time of the first introduction of the disease in 1900 to 1941, only 501 cases with 316 deaths have been reported. These cases have occurred in eight states, the first appearance of the disease was as follows—California 1900, Washington 1907, Louisiana, 1914, Florida 1920, Texas 1920, Oregon 1934, Utah 1936 and Nevada 1937. Up to January 1942 the last two human cases reported occurred in Sukiyou County, California, in June 1941.

### EPIDEMIOLOGY

Geographical distribution.—Plague is now endemic in India, Ceylon, Java, China, and Madagascar.



Figure 1. World map showing the geographical distribution of plague.

A  
B  
C

In China, it is now mainly confined to western Shansi province where the Yellow River flows between this and Shensi province, in which some foci of infection are also present, to Fukien province where in the mountainous areas pneumonic plague also occurs, and to Manchuria. In the first two areas the rat is the main reservoir, whereas in Manchuria other rodents, the marmot or tarabagan, are responsible and the disease is more sporadic, but very liable to develop into a pneumonic epidemic.

It is endemic in the Bombay Presidency, in Hyderabad northern India, in Bihar, the United Provinces and in Assam, no plague has been reported in the southern parts of Madras. It is comparatively rare.

**Epidemic features**—Recent studies in plague have shown that there are two main epidemiological groups, (a) urban and domestic plague and (b) selvatic plague, and that in each of these epidemiological groups the disease may develop from the bubonic to the pneumonic form, when its epidemiology will undergo a corresponding change.

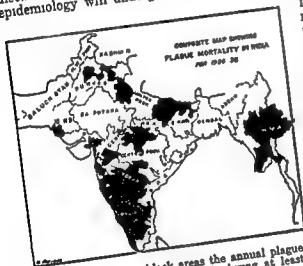


Figure 100 In the black areas the annual plague mortality was over 0.1 per mille during at least one of these years

The urban and domestic form (transmitted from rats) occurs in densely populated areas and spreads along trade routes and overseas in ships. It is primarily bubonic and sporadic, but bubonic plague may assume epidemic proportions and spread like an epidemic disease, though, as will be shown below, it is not a truly epidemic disease\*.

In certain circumstances probably connected mainly with the atmospheric temperature as it occurs most frequently in cold countries, pneumonic form appears and the disease takes on a truly epidemic

form, being transmitted directly from man to man

\*The author is aware that here he is endowing the word epidemic with a special meaning that it does not always convey. The *Oxford Dictionary* quoting from *Sydenham's Society Lexicon* gives the meaning as 'Prevalent among a people community at a special time and produced by some special causes not general present in the affected locality'. This admittedly allows a wider meaning but it goes back a little further to its earliest use (according to the *Oxford Dictionary*) one finds a more restricted meaning. Bacon (1622) 'It was conceived not to be an epidemic disease but to proceed from a malignity in the constitution of the epidemic disease but to proceed from a malignity in the constitution of the epidemic disease but to proceed from a malignity in the constitution of the epidemic disease'.

Language is a living thing and it must be continually growing and changing. Bacon's conception of an 'epidemic' disease as being possibly a divine punishment or a curse or a spell upon the people entirely independent of environment, could be upheld and the *Sydenham Society* gave the word a wider meaning. To do this, its knowledge about epidemic disease is more precise but the word epidemic has precision, its meaning certainly goes far beyond that given to it by the *Sydenham Society* for we have epidemics of malaria in countries where the disease has not continuously for a thousand years. We must therefore invent a new word or restrict the meaning of the old one.

Sylvatic plague (transmitted from wild rodents) that occurs in rural areas and amongst workers in the woods and fields is primarily a sporadic, bubonic plague, but is even more apt to develop into the pneumonic form, when it may be the starting point of a serious pneumonic epidemic (e.g. the Manchurian epidemics of 1910-11 and 1920-21 in which there were about 50,000 and 10,000 deaths, respectively)

**Seasonal and year to year incidence.**—Temperature and humidity have a marked influence on the spread of plague. A moderate temperature, 60°F, and a moderately high relative humidity are considered favourable for the development of the disease. At 70°F, a deficiency of humidity is considered to be a factor in the development of the disease.

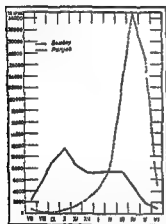


Figure 101 Monthly plague incidence, 1893-1931

As well as the periodic epidemic-like waves of plague, in the production of which many factors are involved, there are in the endemic areas from year to year considerable variations in the incidence, which are associated with climatic variations, and Rogers (1933) has shown that, by studying the past meteorological data, it is possible to forecast whether it will be a good or bad plague year, long spells of abnormally hot and dry weather tend to reduce the incidence during the next plague season, and *vice versa*.

**Age, sex and race incidence**—In the urban and domestic bubonic form, persons of all ages and both sexes are equally susceptible and there does not seem to be any racial immunity. In the pneumonic form, adults, both men and women, who attend the sick, and in the sporadic sylvatic form, men, who are more likely to come in contact

with the sources of infection, are most frequently attacked

The definition of an epidemic (*trans* upon the people) that the writer has adopted for his own use is 'an outbreak of a disease that is transmitted *from man to man*, directly or indirectly but in the transmission of which *man forms an essential link*'.

Application of this restriction on the meaning of the word epidemic does not entail interference with established nomenclature of disease since diseases to which the word epidemic is regularly attached in a defining sense e.g. epidemic typhus, are epidemic diseases in the restricted sense and so-called 'epidemic dropsy' is a misnomer already overdue for renaming, which is only awaiting a definite decision regarding its aetiology.

It would be rational to define endemic (*trans* in or amongst the people) on the same lines, and to use the word sporadic when the disease did not comply with the restriction that 'man forms an essential link'. But the word endemic is already so deeply involved in disease nomenclature, e.g., 'endemic typhus' which is not an endemic but essentially a sporadic disease, according to the suggested definition, that it will be difficult to drop it.

All these epidemiological observations are explainable on the grounds of the known aetiology of the disease which is discussed below

### ÆTIOLOGY

Historical — The disease is one of the oldest known to man who

is a small

pleomorphic

polar staining

**Culture** — It is an aerobe and a facultative anaerobe. It grows easily on ordinary culture medium producing very small round colourless transparent granular colonies in 24 hours at 37°C, increasing to large (4 mm)

the surface, 'stalactites' grow down from the under-surface of the oil globule

There is no hæmolytic on blood agar

**Resistance** — These organisms are killed by drying at room temperature in a day or two, by heat at 55°C in 5 minutes, and by 0.5 per cent phenol in 15 minutes. They survive in the cold almost indefinitely

**Distribution in the body and routes of escape** — Plague bacilli invade the skin causing vesicular or pustular lesions, the local lymphatic system, causing buboes, and the blood stream, in this order, the infection does not however reach and persist in the blood in every case, but when it does the bacilli can naturally be found in every organ in the body. Under certain conditions, the lungs become the site of an intensive infection

In the ordinary septicæmic infection the bacilli do not escape from the body in any of the normal secretions or excretions, but in the pneumonic form they escape in droplets during forced expiration

**Susceptible animals** — Man and both laboratory and wild rodents, and also monkeys are very susceptible, dogs, cats, cattle, sheep, goats and horses are difficult to infect, but most birds are immune

**Toxins** — No true exotoxin is formed, but bacillary filtrates cause severe toxic reactions and immune serum can be prepared by injecting animals (horses) with killed or living cultures

### Transmission

**Historical** — In the historical records of plague epidemics in many countries, it was noted that rats began to die before human beings were affected and the outbreaks in rats and in man were regarded as being intimately connected. The early investigators at the end of the last century failed to follow up this obvious lead and the first Indian Plague Commission (1901) went so far as to state categorically that there was no evidence that the disease was carried by infected rats in ships. In 1897, however Ogata suggested tentatively that the flea might play a part in transmission and in 1898 Simond working in Bombay enunciated the main facts about the transmission epidemiology and control of plague which have remained practically unmodified, to the present day

Lowe (1942) summarizes Simond's contribution to the transmission problem as follows —

'He stated that the introduction of plague rats into a healthy area was generally followed by an epidemic of plague in man but that introduction of an infected man into a healthy area was often not followed by an epidemic. He found that the epizootic preceded the epidemic that it was usually localized in one area of a town to begin with, and that human plague later started in that particular area

He noticed that in about 5 per cent of human cases a primary lesion in the form of a blister containing plague bacilli was seen, and recorded the site in the body of many of these blisters and found that they were most common on the

foot and leg. He considered that the blister was probably at the site of the bite of the transmitting insect. (This is the only observation for which he is usually given credit.)

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to migration of others and to a high degree of immunity of the remaining rats and thought that repopulation of the area by new strains of susceptible rats might cause recrudescence. He also believed that plague might continue to linger among rats in a benign form in the period following an epidemic and that sporadic cases in man might thus be explained.

He stated that the use of rats and also of human habitations for the conveyance of plague by the destruction of which he advocated the use of

Gauthier and Raynaud (1902) narrowed down the issue and transmitted plague from rat to rat by means of the bite of fleas.

Simonds's work was confirmed by the Plague Investigation Commission (1904 to 1913); these workers amplified Simonds's work but added little of basic importance to it.

The primary transmission cycle of infection = rat-flea-rat. The flea becomes infected from the blood of an infected rat, and transmits the infection to another rat by its bite. There are a number of other rodents that are capable of playing the part of the rat in the transmission cycle.

The infection of man is an off-shoot from this primary cycle, and normally, from the bacillus's point of view man constitutes a *cul-de sac*. Man is capable of constituting a link but as only very rarely are bacilli present in human blood in sufficiently large numbers to infect fleas that ingest his blood, and, as the fleas that normally infest man *g* *Pulex irritans* are not good transmitters of plague bacilli man constitutes a very weak link in the mammal-flea-mammal cycle of bubonic plague transmission. Bubonic plague is thus never truly epidemic though the disease may assume epidemic proportions.

In certain circumstances or other climatic conditions the lungs and pleurae are affected, a pneumonia being produced when this has once occurred the



Infection may also take place via the alimentary tract *eg* in Manchuria infection has been caused by the eating of under cooked

epidemiology of the disease

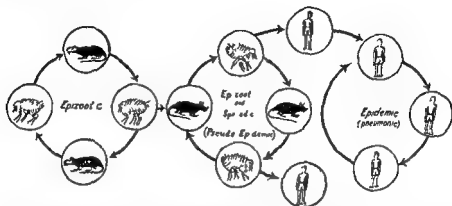


Figure 102 The transmission cycles in plague infection

*Left hand cycle* Brown rat—flea epizootic cycle

*Middle cycle* Black rat—flea epizootic cycle from which man is infected sporadically

*Right hand cycle* Man to man epidemic cycle of pneumonic plague

Infection has been acquired at a post mortem examination and in the laboratory

Finally, the bacillus has been injected with homicidal intent such an instance occurred in Calcutta in 1933 when two accused including one doctor were convicted of murder

#### Essentials for transmission of bubonic plague

The four essentials for the transmission of bubonic plague are thus —

- 1 The plague bacillus
- 2 The rat or other rodent—the natural host and reservoir of infection.
- 3 The rat flea or other flea vector
- 4

Give

variation

(of 2 and 3) susceptibility (mainly of 2 and 3) and environment and habits (of 2 and 4)

pneumonic cases with 31 deaths the reservoir was a squirrel but even here the epidemic occurred in mid winter

2 The rodent Species—There are two main groups of rodents involved in plague transmission (1) rats which in a general way, live in close association with man—though some species live in closer association than others—and are the rodents responsible for the epidemic like

(ii) wild

n plague  
ge brown

(grey) sewer rat, *Rattus norvegicus* Rats of other genera, *Gunomys* and bandicoots, are also susceptible, but from their habits are a less important menace to man

(ii) The tarabagan or marmot (*Arctomys bobac*) and several species *Citellus* (Suskiks) in the Caucasus Siberia and Manchuria, the jerboa in southern Russia, the gerbille and the multimammate mouse, *Mastomys coucha*, in Africa, and the ground squirrel (*Citellus beecheyi*) in California, are the most important reservoirs of selvatic plague

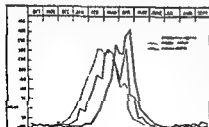
The rat-factors determining incidence these are—

experience of the rat population

(b) *Habits* the reservoir of infection must come into close association with man, by natural inclination and/or by opportunity This factor will depend on the species again, and on the environment

(c) *Density of the rat population*, the disease will not assume epidemic proportions unless there is a sufficient number of susceptible rats living in close contact with man The rat index calculated from the number of rats caught in a given time in one hundred standard traps must be at least 50 The rat index will depend on environment and food supply

The development of conditions for an outbreak of plague in man — The usual sequence of events is as follows — The grey rat, which infests docks and generally from his habits makes more contacts with the outside world is the first to become infected one such rat acquires plague and dies, its fleas leave the dead body and parasitize other rats to whom they transmit the infection, and so a grey rat epizootic develops In time a certain number of fleas from the plague-infected grey rats infest the more venturesome amongst the black rats and the epizootic spreads to the domestic rat population Infected fleas are thus brought into man's habitations, and when the rat population becomes reduced the fleas from a dead rat failing to find another rat begin to infest man and when this incident is repeated many times an outbreak, which assumes epidemic proportions, occurs amongst the human population (see figure 103)



In course of time a point arrives when the whole rat population has been infected a large number have died and the rest have recovered and are immune, so that the epizootic and the human outbreak come to an end Epizootic conditions cannot arise again until a new generation of non immune rats grows up However, over a



that fleas from these squirrels should be taken into the houses by other rodents which are themselves perhaps not susceptible or by domestic animals or that an epizootic should arise amongst rodents that do frequent human habitations. For these reasons large sums of money have been spent on rodent destruction in that country.

The infection in the flea's gut also passes forwards and eventually a massive infection may block the pharynx of the flea. When the flea attempts to take another blood meal the blood will not pass this plug of bacilli which have to be ejected by a regurgitatory effort and the bacilli are thus injected into the flea's proboscis into the new host. A third method by which the flea transmits the infection is by contamination of its mandibles whilst feeding on an infected host and direct transference of the *matres morbi* to another host. Of these three methods the second is almost certainly the most important.

Only a comparatively small percentage of fleas feeding on an infected rat will become infected and of those that become infected only a small percentage will transmit the infection. The percentages vary according to circumstances.

The flea factors determining incidence these are—

(a) *Efficiency of the flea as a transmitter* which will vary according to (i) species and (ii) environmental (climatic) conditions under which it lives.

(b) *Longevity of the flea and maintenance of infection* which is again

(d) *Density of flea population* which will depend on the climate and the rat population varying directly with the latter. This is measured by a flea index which gives the average number of fleas on each trapped rat. A cheopis index of at least 3 appears to be necessary for epizootic conditions.

(i) *Species*—The most important transmitter of rat borne plague in the tropics is *Xenopsylla cheopis*. Another rat flea *Xenopsylla astia* also common in the tropics is capable of transmitting plague but is a relatively poor transmitter and reaches epidemic proportions long so that in endemic areas season. Another relatively poor transmitter is *Leptopsylla segnis*. (The low incidence of plague index *X. astia* being the common flea.)

In temperate countries *Nosopsyllus fasciatus* and *Leptopsylla segnis* are the important transmitters.

*Pulex irritans* the flea that commonly infests man is capable of transmitting the infection (*vide supra*) as are many other fleas such as the dog and the cat fleas *Ctenocephalus canis* and *Ctenocephalus felis*.

The other rodent carriers have their various fleas most of which will in special circumstances bite man and are capable of transmitting plague.

For example, *Ceratophyllus tesquorum*, of the marmot will show the 'blocking' phenomenon, if fed - and *Xenopsylla eridos* of the *Diamanus montanus* of the mitters

(ii) **Environmental (climatic) conditions**—These have a marked effect on the flea *X cheopis* breeds best at a temperature between 68°F and 77°F, and in the presence of a high degree of humidity. Above 85°F not only does breeding slow down, but this high temperature adversely affects plague-infected fleas, so that as the temperature rises, transmission decreases and eventually ceases. Humidity is also an important factor, and in the tropics a saturation deficiency of less than 10 millibars is necessary for effective transmission under dry conditions 'blocked' fleas rapidly die. Thus, the

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important one, and it has been shown that in deep rat burrows, temperature and humidity may remain suitable for flea survival and transmission of infection long after the surface atmosphere has become quite inimical to both. It is believed that it is by this means that infection survives the hot dry season in some places (George and Webster 1934). Conversely, in cold countries fleas may find micro climates, e.g. in houses and in ships, which are warm enough for them.

Where other fleas are the transmitters, the ranges of temperature and humidity ideal for transmission may be different but

4 *Man* is the evidence of any differences in

The density of the human population will of course influence the actual number of cases in a particular area, but overcrowding will only lead to an arithmetical and not a geometrical increase as would be the case in (note, p 324). As however, overcrowding is a condition in which rats are likely to be found, transmission of infection will be encouraged. If man's environment is such that it provides food for rats and to encourage a close association between rats and man the conditions will be favourable for a plague to be introduced.

Plague is maximal when the infection is introduced in conditions most favourable that is where *R. rattus* is the predominant rat and is abundant where *X cheopis* is the

### Spread of infection outside endemic areas

Plague is carried by fleas, and is spread by the flea *X cheopis* which is carried by the rat *R. rattus*. The ability of the flea to survive in grain bags, gunnies etc., for long periods even under unfavourable external atmospheric conditions, has only recently been fully appreciated and it is believed that this mode of

transfer of infected fleas plays an important part in carrying infection from place to place

### PATHOLOGY

**General reaction to infection**—There are three lines of defence against the invading bacillus (a) the skin, (b) the lymphatic glands, and (c) the humoral antibodies in the blood. If the bacilli are held up at the first line of defence, namely the first group of lymphatic glands to which the lymphatic vessels pass, the glands will be enlarged. If the bacilli pass the second line they reach the blood stream in small numbers at first, and are distributed widely in the body where, exercising their affinity for lymphatic glands, they affect these mainly causing a general adenitis, the infection may be overcome by the humoral antibodies in the blood and the bacilli will reappear in the blood only as temporary showers. If, on the other hand, they overcome the humoral antibodies in the blood, they will cause a septicæmia.

The invasion of the lung parenchyma is also probably a matter of local resistance, as well as of some natural or acquired intrinsic quality in the bacilli themselves, but this appears to the writer to be an incident outside the natural sequence of invasion.

The local lesions are the clinical manifestations of an acute inflammatory reaction, and a rapid passage of the defences indicates a failure of the local resistance. Hence, the local vesicle or pustule is more commonly seen in ambulant cases or in cases of *pestis minor*, and clinical buboes are usually absent in the severe septicæmic cases, though at post-mortem examination the glands will be found slightly enlarged.

**Morbid anatomy.**—There is usually a post-mortem rise of temperature and early decomposition: there may be ecchymoses all over the body and submucous hæmorrhages.

The plague toxin has a particular affinity for the endothelial cells of arterioles and lymphatics, in these, it causes degenerative changes which lead to extravasation of blood into the tissues. All the organs are congested and there are numerous hæmorrhages in the solid viscera into the lumina of the hollow viscera, and into serous cavities.

In bubonic and septicæmic plague the lymphatic glands are enlarged, red and congested, and surrounded by a hæmorrhagic œdema. Histological sections show a hyperplasia, invasion by large numbers of bacilli which are multiplying, small necrotic areas into which hæmorrhage has taken place, and often small abscesses. The spleen is enlarged, it is congested

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pericardial effusion

In pneumonic cases, there is a hæmorrhagic pleurisy, and the alveoli are filled with a hæmorrhagic exudate. The inflammatory condition extends to the bronchioles, the bronchi, and even the larynx and trachea, and the bronchial lymphatic glands are involved. It is usually a central pneumonia.

The blood picture—There is never any anæmia except in the chronic suppurative stages of the infection, on the contrary, the great dehydration in the early stages may lead to polycythæmia. A leucocytosis is almost invariable except in the very severe pneumonic cases when paradoxically it may be absent. The count often rises to 20 to 25 thousand leucocytes per c mm, or even higher, with an increase in the percentage of lymphocytes and a decrease in large mononuclears, at first, but later there may be a relative as well as an actual granulocytosis.

In severe septicæmic cases, bacilli may be present in the blood in sufficiently large numbers to make it possible to find them in an ordinary blood smear.

The urine—This is scanty and highly coloured. It usually contains an appreciable amount of albumin, except in very mild cases. The urea, uric acid and chloride excretion are reduced. A few red blood cells are commonly seen, and there may be obvious hæmaturia.

Suppression of urine may occur in severe cases, when there is much dehydration and a low blood pressure.

### SYMPTOMATOLOGY

**Clinical types**—These have been foreshadowed in the preceding paragraphs, there are five main clinical types—

(i) *The ambulant* in which there is only a vesicle at the site of invasion with a little local lymphangitis and no constitutional symptoms.

(ii) *Pestis minor*, in which there is a single gland or a single group affected and only mild constitutional symptoms.

(iii) *Bubonic plague* in which the local group of glands mainly but also other glands in different parts of the body are affected and there are usually grave constitutional symptoms.

(iv) *Septicæmic plague* in which there is an established virulent septicæmia and usually a rapidly fatal course.

(v) *Pneumonic plague*.

The so called cellulo cutaneous type which is now relatively rare but from historical records appears to have at one time been the common form may occur in either the bubonic type in which the local cellulo cutaneous lesion corresponds to the bubo, or in the septicæmic type, it is probably more common in the latter.

It should perhaps be emphasized that there is no sharp line of distinction between the bubonic and the septicæmic types, if there is a general adenitis, there must at some time have been a bacillary shower in the blood. In the severe bubonic type, these showers are probably repeated frequently, it is only when the bacillary invasion overcomes, though perhaps only temporarily, the humoral antibodies in the blood that a septicæmia is established.

The first two types need no further description.

#### *Bubonic and Septicæmic Plague*

The incubation period is from two to eight days, rarely longer, the average is about four days.

There are sometimes prodromal symptoms for a day or two with malaise, anorexia, apathy, headache and possibly aching pains in the groin, or elsewhere at the site of the subsequent buboes. Usually however the onset is sudden, with a rigor and a temperature rising to

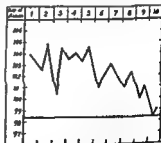


Figure 105 Temperature chart in a case of bubonic plague





Another complication is septic pneumonia, which will often develop in a debilitated patient with open sinuses, this condition should not be confused with pneumonic plague

### *Pneumonic Plague*

The c  
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eventually develops the classical 'prune-juice' colour and consistency. The patient has an anxious expression. There is not usually much pain in the chest but the patient is cyanotic and some dyspnoea develops early. The physical signs are not characteristic of pneumonia, there is little the vocal resonance is unchanged but

is to the right of the sternum and the  
blood pressure is low. The pulse rate  
becomes uncountable. Death  
and it is seldom deferred

the form of submucous  
hæmorrhages purpuric spots epistaxis hæmoptysis hæmatemesis, hæma-  
turia and/or melenæ

### DIAGNOSIS

**Clinical**—A typical case of severe bubonic or septicæmic plague presents a characteristic picture the sudden onset high temperature rapid pulse, great prostration bloated appearance and conjunctival suffusion the slurred speech and staggering gait the apathy and mental confusion and eventually the buboes in the former, are not likely to be confused with any other condition except possibly typhus if the buboes are late in developing

**Bacteriol** (i) direct  
examination (ii) inoculation

From the primary vesicle of the ambulant case or the bubo of pestis minor, material can be obtained by gland puncture in the latter case for direct examination or culture animal inoculation will usually be unnecessary as the organism will in most instances be uncontaminated by other organisms. In the early stages of bubonic plague the same remark applies but later when the glands suppurate it will often be necessary to resort to animal inoculation to confirm the diagnosis.

In septicæmic plague—and it must be remembered that all bubonic cases are potentially septicæmic—the organism can be obtained from the blood rarely by direct examination but always by culture and animal inoculation.

In pneumonic plague the plague bacilli are present in large numbers in the sputum they can be recognized in a direct smear but it will be advisable to confirm the finding by animal inoculation whenever possible, as culture will be more difficult on account of contamination.

**Outline of technique**—(i) Smears should be stained with Gram's stain and methylene or thionin blue. *Pasteurella pestis* is gram negative and the characteristic bipolar staining will be easily recognized but confirmation of the identity of the organism should always be obtained if possible this is essential where one is dealing with an isolated case.

(ii) To obtain a culture, inoculate blood sugar plates (pH 6.8 to 7.2) and broth tubes with gland juice. Blood from the finger may be inoculated directly on to a plate or 5 ccm from a vein into 100 ccm broth flask. The broth and plates should be kept at 22°C or at room temperature except in very hot or

cold climates. On the plate delicate translucent dew-drop colonies appear, these are sticky and can be pushed along the surface of the plate. The broth should show a pure growth.

The certain identification of the culture is complicated by the fact that the plague bacillus is difficult to emulsify so that serological identification is almost impossible. Animal inoculation is usually considered essential.

(iii) For animal inoculation it is best to use two white rats and two guinea-pigs. Some of the material should be inoculated subcutaneously into the groin and some rubbed into a shaved area on the abdomen of one of each species. The latter procedure is important because if the material is inoculated subcutaneously the contaminating organisms may kill the animal before the plague infection develops. In a positive case the animals will die of plague septicaemia within 3 to 5 days. (Animals must be kept in insect proof cages during these tests.)

The animal dying of plague will show general subcutaneous congestion and a fibrinous exudate in the peritoneum and locally necrosis of the tissues, hæmorrhagic oedema, and the lymphatic glands enlarged and buried in hæmorrhagic oedema. At the site of the percutaneous inoculation i.e. the shaved area there may be umbilicated pustules. In the guinea pig miliary necrotic nodules will be seen on the surface and throughout all the organs. Pure cultures of plague bacilli will be obtainable from most of these sites.

For the identification of the cultures of *Pasteurella pestis* 0.1 ccm of a 24 hour broth culture should be inoculated intraperitoneally, the animal will die in two or three days.

**The agglutination test**—This test is of no value in the diagnosis of plague for the reason stated above, namely the difficulty of obtaining a

here

As mentioned above a septicæmic or a severe attack before the buboes develop may be mistaken for typhus and of course any other severe toxæmic condition, the typhus rash should be looked for, but it appears too late to be of any real value.

## PREVENTION

Prevention has to be considered under two main headings —

(A) *The prevention of the introduction of plague into a non-endemic area*

(B) *The control of plague in an endemic area*

The reader is referred back to p. 328 where the transmission cycle is discussed.

A. *The prevention of the introduction of plague into a non endemic*

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other factors. For example, it will always be worth controlling the rats in dock areas in any country, but on the other hand prophylactic inoculation of the population where plague has not yet occurred would be a waste of energy.

have to be made

■ The control of plague in an endemic area —If this cycle can be broken at any point, plague will not occur, if it can be weakened, plague will be reduced

In pneumonic plague the infection is passed from man to man (see figure 102, p 328, right-hand cycle), isolation of the sick is therefore essential to protect the general population, doctors, attendants, and nurses must be protected from droplet infection by masks and other measures, and the community as a whole should be protected against the effects of infection, by prophylactic inoculation

In the transmission of bubonic plague, man does not constitute an essential link (see figure 102, middle cycle) and, in an outbreak, infected man is an almost negligible factor as a reservoir of infection, for the reasons that the septicaemia seldom reaches the degree necessary for transmission, and that his fleas are poor transmitters. Isolation and treatment of the  
an outbreak  
pneumonic  
measure a

reasonable precaution

If, however, the rodent-flea-rodent cycle is broken, by attacking the rodent-flea or the rodent, or both, the epizootic will cease and the sporadic infection of man will no longer occur

Prevention must therefore be considered under the following headings —

- 1 Isolation and treatment of the sick
- 2 Measures against rats or other rodents
- 3 Measures against fleas
- 4 Protection of man from rats and fleas
- 5 Prophylactic inoculation

1 Isolation and treatment of the sick —There is little more that need be said here under this heading, except it must be remembered that it is mainly against droplet infection in pneumonic plague that protection has to be given to attendants, so that the hospital rooms should be light and airy and wherever possible some form of screen protection should be provided for the personnel

■ Measures against rats or other rodents —These measures will constitute insurance against plague infection in any country, but they are naturally more important in an endemic area, and they must be intensified in the presence of an outbreak or when an outbreak is threatened

A plague epizootic amongst the local rat population, or a high infection rate amongst fleas, is the danger signal, and an efficient public health department will, so to speak, keep its finger on the pulse of the rat and flea populations, so that where and when conditions are most favourable for an outbreak the measures may be concentrated

A large number of deaths amongst rats, or of 'rat falls' as they are

Rats will only multiply as long as they are provided with harbourage and food, and the construction of rat proof buildings and particularly rat-proof grain stores is an important measure of prevention of plague. Other general measures include the proper disposal of refuse, the provision of covered receptacles for household garbage, and the rat-proofing of the sewage system.

The domestic cat is a valuable assistant in keeping down the rat population in warehouses, ships, etc.

Rat destruction will of course form an important part of the programme. There are many methods, these include trapping, poisoning, infecting with Danyss virus, and gassing. The last-named is by far the most effective.

There are many forms of rat trap; some kill the rats, others capture them alive. It should be remembered that the fleas leave a dead rat, therefore during a plague epizootic it is advisable to use traps which keep the rats alive or which destroy the fleas as well. Rats must then be killed in such a way that their fleas are also killed, or the body should be immediately plunged into strong phenyl or other disinfectant. The dead rat is a grave danger and should be handled only by specially protected personnel.

If the rat-flea population is to be investigated, it will also be necessary to capture the rats alive. They are then chloroformed or placed in a gas chamber, this will kill the fleas also. The fleas are then combed out, counted, and identified.

There are innumerable rat poisons. These again should not be used during an epizootic. Many of them are dangerous to cattle and other animals, and are therefore of limited use. Barium carbonate is however a useful poison because one to two grams will kill a rat, which usually goes into the open—in search of water—to die, whereas dogs can take up to

Gassing has to be carried out by trained squads, but it is by far the

fumigate 100 cubic feet of hold, or warehouse.

For rat burrows, an easier way is to apply the cyanogen gas in the form of a powder from which the gas is given off either slowly or rapidly.

Cymag is such a powder made by Imperial Chemical Industries. It contains 20 per cent hydrocyanic acid, and the gas is given off slowly. Another form is 'calcid briquettes' which are ground up into a powder and blown into the holes. In these cases, all the holes must be effectively blocked up before the gas or powder is pumped in, or the rats escape, this applies particularly to the powders that give off the gas slowly.

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with 5 drachms of mustard oil are made into a paste, to this a drachm of

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dioxide which kills rats, but it not so effective against fleas

The measure to be adopted against other rodents will naturally depend on the rodent concerned

In the United States a very elaborate system of investigation of wild

It is probably this vigilance

the past (vide supra)

country movements of rats is

quarantine regulations are

of ships. The effect of such

that, whereas 50 per cent of ships arriving at Atlantic ports were rat-

infested between 1925 and 1927, the percentage had dropped to 8.4 per cent

in 1937

The danger is from shore-rats going on board at the infected ports,

Therefore, ships lying along-

the dock, all

discs at least

angles to the

fresh tar and

hawsters, and

should be raised at night when not in use

3 Measures against fleas—Most of the gassing measures are as

effective against fleas as against rats, and there are few measures that are

designed to destroy fleas independently of their rat hosts, as suggested

above, care should be taken, when rats are killed, that their fleas perish

with them, and both trap and rat should be placed in disinfectant

The floors and particularly the corners of rooms where rats have been

found should be pyrethrum sprayed, the strength used for mosquitoes

(qv), namely, a one-in-twenty dilution in kerosene of the usual con-

centrated pyrethrum extract, will be suitable

Clothes and bedding that are suspected of harbouring fleas can also

be sprayed with this

Fleas are likely to be carried from place to place and country to

country in grain bags, cotton and jute bails, gunny rolls, etc., and suitable

disinfection of any such material coming from an active endemic area

should be carried out

4 Protection of man from rats and fleas—The building of rat-

proof houses is much easier than the rat-proofing of existing houses. The

main points in a rat-proof house are that the lower walls and floors should

be of hard brick and concrete respectively, and that the former should

sink at least two feet into the ground to prevent rats burrowing under it. All ventilators and drains must be protected by iron gratings.

During a plague epidemic, evacuation of all infected houses as indicated by 'rat falls' as well as by human cases is an important measure. The occupants should not return for several months and then only when the house has been shown to be plague-free by placing caged guinea-pigs in the house for several nights, if they survive the house is probably free from infection.

For those working in a plague-infected area and especially those employed on plague duty the clothing should be carefully selected. White is preferable, as fleas can be seen easily and picked off. Fleas can but do not as a rule bite through clothes. The clothes should be such that fleas cannot get inside them, therefore trousers and shorts are unsuitable and should be replaced by knee breeches or 'jodhpurs'; gum-boots give good protection but the tops should be closed, the sleeves must be tightly bound round the wrists and those handling rats must wear leather or rubber gloves, and an open neck is also a danger, as fleas may fall from the roof.

### 5 Prophylactic inoculation —

**Historical**—Haffkine introduced the inoculation against plague at the end of the last century during the last great pandemic. This was the first occasion on which a vaccine had been used on a large scale as a public health measure. He used a six weeks-old heat-killed ( $65^{\circ}\text{C}$  for one hour) culture of *Pestis* in broth to which 0.5 per cent phenol had been added and gave 4 ccm to an adult. Figures collected by the Plague Commission suggested that this inoculation caused an 80 per cent reduction in the infection rate and an 80 per cent reduction in mortality amongst those infected. Since this date many millions of doses of this vaccine have been given in India and elsewhere but the statistical value of some of the data that was collected by the Plague Commission and later has been questioned.

In 1907, Strong working in the Philippines used a live avirulent strain of plague as a vaccine but this vaccine did not come into general use until 1935 when de Vogel and Otten re-introduced vaccination with an avirulent living culture of plague. It has been reported that the immunity produced by this live strain is much higher than that produced by a dead virulent culture. This live avirulent strain has now been used in Java for some years and over two million doses given without ill-effects.

Although it is not yet finally settled which is the more effective the modified Haffkine vaccine now used in India or the live avirulent vaccine of Otten now used exclusively in Java, Madagascar, and elsewhere at present the indications outside India are all in favour of the latter whilst in India the policy at present is to trust a well-tried friend. This policy has been influenced by the fact that avirulent live vaccines tend to deteriorate rapidly, so that there would be great difficulties in the way of maintaining stocks and distributing them to the people in India.

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severe than with most vaccines. The vaccine provides protection for six to eight months.

## TREATMENT

Good nursing will play a very important part in determining the recovery of the patient. He should be confined strictly to bed and not be allowed to do anything for himself, he will want plenty of fluid, possibly drip-feed intravenous glucose, and frequent fomentations to the buboes. Further, such possible emergencies as hæmorrhage from septic erosion of large vessels may have to be met.

The treatment may be considered under the headings, (a) *symptomatic*, (b) *local*, and (c) *specific*.

**A Symptomatic treatment**—The treatment is that for any asthenic febrile disease, for hyperpyrexia, hydrotherapy should be employed, and antipyretic and depressant drugs avoided, the diet should be fluid but nourishing, but since the disease is a short one, it is not necessary to force the calories though the patient should be encouraged to drink freely, imperial drink, barley water, or glucose water. Intravenous glucose, 5 per cent, can be given fairly rapidly if there is a lowered blood pressure, but otherwise by the drip-feed method almost continuously.

For the generalized pain and restlessness, phenobarbitone should first be tried, and, if this fails, morphia may be given judiciously. Digitalis and

oil, or cardiazol

**B Local treatment**—The buboes may play an important part in the more vigorous local treatment. The fever subsides, and these may cause a There was an old teaching that it was

missible to put in a scalpel to relieve the pressure and pain. When they

pyrimine in therapeutic doses by mouth at this stage is also useful. If these sinuses are allowed to become secondarily infected, the course of the disease may be prolonged for weeks or even months.

**C Specific treatment**—The present indications are that serum treatment is likely to be replaced entirely by chemotherapy in the near future.

**Serum treatment**—Yersin's serum has no direct action on the 'anti-infectious' infection in an

n after excluding a group of cases for various reasons, a procedure which is always open to suspicion, it has seldom been possible to show more than about a 10 per cent improvement in death rate, e.g. from 74 per cent in 200 controls to 63.5 per cent in serum-treated cases. Recently, Sokhey (1936) has produced an anti-serum which has proved more efficacious, and in several series the death rate has been of the order of 25 per cent, with the control series showing about a 50 per cent death rate.

The initial dose recommended is usually for 50 to 100 c cm, and this must be repeated daily until the temperature is normal.

**Chemotherapy.**—Prior to the introduction of the sulphonamide drugs, many drugs had been tried without any conspicuous successes, e.g. intravenous iodine, mercurochrome, germanin.

Schütze (1939) demonstrated the efficacy of sulphapyridine in plague-infected rats and mice, and Wagle *et al* (1941) obtained good results in human plague with both sulphapyridine and sulphathiazole, their death

doses, and there is an obvious possibility that some of the newer compounds, e.g. sulphadiazine, may prove more efficacious.

### PROGNOSIS

This of course will depend on treatment to a large extent.

The pneumonic form is always fatal.

In published series of treated cases, the control series always have death rates between 50 and 75 per cent. In such series, ambulant cases and cases of pestis minor will probably not be included, so that the gross death rate is probably less.

The prospects of the patient depend on his resistance, and can be measured by the degree of septicæmia from which he suffers. In cases with uncontrolled septicæmia and large numbers of bacilli in the blood, the death rate is probably 100 per cent, but, in bubonic cases with only bacillary 'showers', it is between 25 and 50 per cent.

In the septicæmic case, the patient usually dies within the first five days. Hence the prognosis should always be guarded, as recovery sometimes occurs in a patient who

Death may take place after several weeks with delayed complications.

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Histopathologically, the local lesion shows a necrotic centre surrounded by an area of polymorphonuclear infiltration, outside which there is some lymphocytic infiltration of the surrounding tissues. A similar change occurs in the affected organs, in the lungs, outside the necrotic focus there is a zone of alveolar exudate, and the inflammatory changes may involve the whole lobe and the pleura, and in the liver, the parenchyma cells are invaded and destroyed by *Bact tularensis*, and appear as bags of organisms.

More chronic lesions which resemble tuberculosis are sometimes observed. The necrotic centre is surrounded by an area of epithelioid cells and fibroblasts, outside which is a zone of lymphocytic infiltration, scanty giant cells may be found in these lesions.

**Blood picture**—A moderate leucopenia is the rule, and even in the pneumonic cases the leucocyte count is seldom above 10,000 c mm.

### SYMPTOMATOLOGY

**Clinical types**—The usual classification refers to the ulcero-glandular, oculo-glandular, glandular and typhoid types, but this classification is neither satisfactory nor comprehensive. In our probably incomplete state of knowledge regarding the scope of *Bact tularensis* infection, it will be unwise to adopt any fixed classification, for, as our experience of this disease widens, a satisfactory one will probably evolve.

The clinical picture shows considerable variation according to the mode of entry of the causal organisms. The most typical symptomatology, and the one that is described below, occurs in those cases in which infection enters through the skin, either through an abrasion or by the agency of an insect, causing a local ulcer and local glandular infection. If it enters through the conjunctiva, this structure is first involved and the clinical picture is that of an oculoglandular type, generally in this type

enlargement or a septicæmia, and produce an attack of the so called 'typhoid type'. This latter is also the form that the disease usually takes when the infection is acquired by eating insufficiently-cooked infected rabbits.

Cases have been reported in which meningeal symptoms developed early and the meninges were shown to be infected with *Bact tularensis*.

Finally, there is the clinical type in which pneumonia is a primary manifestation, as distinct from the pneumonia which may develop as a complication in any severe form of tularemia. On analogy with plague and from suggestive epidemiological reports, it seems possible that in some of these cases there is a primary infection of the lung.

**The clinical course**—The incubation period is in the large majority of cases from three to four days, the extremes are 24 hours and ten days. The onset is sudden with general symptoms, headache, fever with chilliness, vomiting, prostration, and pains all over the body, very suggestive of influenza or a sub-typical dengue. The next day, or sometimes earlier, the local lesion which now develops into an ulcer, and is enlarged and painful. The fever rises in 24 hours, after two or three days the temperature falls or even to normal for one to three days, and then relapses as a high continued or remittent fever (see figure 109), accompanied by fairly profuse sweating, loss of weight and increasing

debility, usually followed by  
convalescence is very

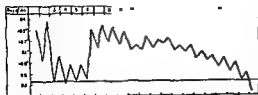


Figure 109 Characteristic chart of uncomplicated tularemia

course of the infected lymph channels, these persist as hard tender movable lumps for some months and occasionally they break down.

A rash is sometimes reported but it is not constant, nor characteristic either in its time of appearance or form.

The spleen may be slightly enlarged.

In the primary pneumonic form the onset is usually with a cough, pleuritic pain, headache, general malaise and a sharp fever usually with chills. The temperature continues as a high remittent fever (see figure 110) with periodic chills. The physical signs are sometimes atypical, and the pleural effusion masks the x-ray picture so that the diagnosis is frequently postponed until the autopsy. Milder examples of this type are probably very frequently missed but, judging from the reported cases, one must consider the prognosis very bad.

**Complications.**—The commonest are those associated with the local lesions and the glandular infections. Ulcers and the sinuses that result from suppurating glands may become secondarily infected and persist for months. The local eye

out convalescence, or at an early date the glands may become necrotic, suppurate, and eventually break through the skin leaving a sinus that may not heal for many months. Subcutaneous nodules may form along the

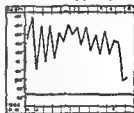


Figure 110 Chart of a fatal case of pulmonary tularemia (Kennedy)

(vide supra)

#### DIAGNOSIS

The circumstance may lead one to suspect that a febrile illness is tularemia, when for example the patient has been bitten by *Chrysops discalis* in an endemic area, or has been on a shooting expedition when he has been in contact with the animal. On the other hand, many cases have occurred in which the mode of infection was completely obscure.

Clinically the combination of a local lesion or conjunctivitis with tenderness and pain in the lymphatic system is characteristic.

**DIFFERENTIAL DIAGNOSIS**

The pneumonic type will be particularly hard to diagnose clinically, except that it is a slightly atypical pneumonia with pleurisy, which does not respond to the usual chemotherapeutic agents or to serum.

Bacteriological evidence is of course the most desirable, but is not at all easy to obtain. On media inoculated with the blood or gland juice growth has been obtained, but not readily, and animal inoculation is the surest method. Two to five cubic centimetres of defibrinated blood diluted with an equal amount of normal saline inoculated intraperitoneally into a guinea-pig will produce an infection that will kill the animal within three or four days, with the production of the typical lesions from which

b test, but this will mostly  
fc 1 in 80 by the third or  
n 5 000 in convalescence  
The titre falls slowly, and agglutinins have been reported to persist up to 33 years. Sometimes the sera will also agglutinate *Br. melitensis* and/or *abortus* (vide supra).

An intra dermal test in which 0.05 ccm of a bacterial suspension produces a wheal five millimetres in diameter in a positive case, has had a few advocates, it gives a positive result at an earlier date, but it is probably less specific than the agglutination test.

### PREVENTION

A study of the methods of infection will immediately indicate a number of ways in which the dangers of infection can be obviated, or at least reduced (vide supra).

As there is considerable danger of laboratory infection, very special precautions should be taken with regard to the handling and isolation of inoculated animals, e.g. rubber gloves should always be used.

Prophylactic inoculation has not proved entirely satisfactory hitherto but recently Foshay *et al.* (1942) have shown that some protection is given by inoculation with dead cultures, and that infections in inoculated persons are milder.

### TREATMENT

No really successful specific has yet been found. Serum treatment has been used extensively, and the results of treatment in 600 cases with a similar number of controls have been reported (Foshay, 1938). The results were not very striking, the death rate was 4.2 per cent in the treated cases, but Foshay considered that they demonstrated the value of the serum.

Otherwise the treatment is symptomatic. Surgical interference with the enlarged glands or the nodules is not to be recommended, open local lesions should be treated with hot saturated magnesium sulphate compresses.

### PROGNOSIS

During 1938 and 1939, there were about 4,300 cases reported in the United States, with a death roll of about 290, a rate of approximately 6.7 per cent.

From the point of view of invalidism, it is a serious disease, as full health is seldom restored under 3 to 4 months, and the average period of hospitalization is often reported as over 100 days. In some cases, chronic sinuses have persisted for two years.

The cases in which infection was conveyed by eating undercooked rabbits seem to be more serious, and a 60 per cent death rate is reported in one such series.

Pulmonary complications cause deterioration in the prognosis, it is reported that 30 to 40 per cent of patients with these complications die, and more than half the patients who die are in this group. The death

rate amongst patients with primary lung infections appears to be even higher. Those in which meningitis occurs always die.

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man from animals by various means

Historical — The earliest attempt to separate the first recognized form of this fever from the second was made by B. Bang in 1861. He isolated the causal organism of the cattle disease and in 1914 Traub isolated a similar organism from pigs. In 1918 Alice Evans demonstrated the close antigenic relation between the causal organism of Malta fever now known as *Brucella melitensis* and the causal organism of contagious abortion in cattle and in pigs now known as *Brucella abortus* and *Brucella suis* respectively and in 1920 the generic name *Brucella* was adopted.

Fever Commission was sent out under the auspice of the British Government to investigate the means of spread of the disease they discovered that goats were the reservoir of infection and that the disease was spread mainly by the agency of goats milk.

Contagious abortion was recognized as a disease of cattle early in the 19th century in Great Britain. In 1897 Bang isolated the causal organism of this cattle disease and in 1914 Traub isolated a similar organism from pigs. In 1918 Alice Evans demonstrated the close antigenic relation between the causal organism of Malta fever now known as *Brucella melitensis* and the causal organism of contagious abortion in cattle and in pigs now known as *Brucella abortus* and *Brucella suis* respectively and in 1920 the generic name *Brucella* was adopted.

Shortly afterwards Bryan in Rhodesia and Kleefer in America recognized certain of the undulant fevers in man in these two countries as abortus fever transmitted from cattle and pigs respectively.

Discussion — In our present state of knowledge it seems justifiable to separate this group into the original Malta fever caused by *Br. melitensis* and abortus fever caused by *Br. abortus* and *Br. abortus* var *suis* (or *Br. suis*), as there are epidemiological and clinical differences between the two diseases.

## MALTA FEVER

Definition — Malta fever is a specific disease characterized by fever which may run a prolonged undulant course effusion and pains in the

joints, and an enlarged spleen, it is caused by *Brucella melitensis*, and it is conveyed to man in the milk of goats, amongst which the infection is enzootic, and by other means.

## EPIDEMIOLOGY

**Geographical distribution**—Malta fever has a wide distribution and will be encountered in all the zones, except possibly the arctic but the largest numbers of cases occur in the sub-tropics.

It is rife in the islands of the Mediterranean and in all the countries of the Mediterranean littoral, and it occurs in many other European countries. It occurs in the southern states of America, in Mexico, and in South America, in South Africa in Iraq, Iran and northern India, in China, the Dutch East-Indies, and the Philippines, and in northern Australia.

**Epidemic features**—The infection is an enzootic affecting goats and to a less extent other animals, and is transmitted sporadically to man by the ingestion of goat's milk or goat's milk products, and possibly by other

it has shown a tendency to rise again. The indigenous population also suffered, but they were usually affected in childhood when the disease is likely to be milder.

likely to be involved in the process of the cell's death. The cell's death is a process that is controlled by the cell's internal machinery. The cell's internal machinery is a complex system of proteins and enzymes that work together to regulate the cell's life cycle. The cell's internal machinery is a complex system of proteins and enzymes that work together to regulate the cell's life cycle. The cell's internal machinery is a complex system of proteins and enzymes that work together to regulate the cell's life cycle.

The incidence varies from year to year and is very definitely seasonal in Malta it occurs in the hot dry months of the year, June to September (see figure 111). This seasonal incidence, which is also noted in other endemic areas, e.g. south-east France, where it is a little earlier in the year, is explained on the grounds that it corresponds with the kidding or lambing seasons, but there are other possible explanations (*vide supra*).

Persons of all ages are affected and the highest incidence is between the ages of six and thirty. Men are said to be most affected, but this may be due to the occupational factor.

The disease has an occupational distribution and is common amongst goat-herds and dairy and farm workers

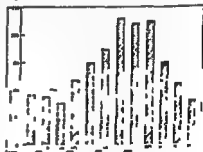


Figure 111 Seasonal distribution of  
Malta fever (Huddleson 1939)

## ÆTIOLOGY

The causal organism—When first described by Bruce, the causal organism was named *Micrococcus melitensis*, but later when its relation to the other organisms causing undulant fever was recognized (*vide supra*), the genus *Brucella* was created and this organism was renamed *Brucella melitensis*.

*Br melitensis* is a coccus-bacillus 0.3  $\mu$  to 0.5  $\mu$  in diameter, with oval or even bacillary forms which may be as much as 2.0  $\mu$  in length. It is non-motile non-sporing and occurs singly, in pairs or even in short chains. It is gram-negative.

Culture—It grows on ordinary nutrient agar but very slowly, it will grow better on a special medium. It grows at 37°C.

months. It will survive for many months in laboratory medium. Laboratory infections are relatively common.

Pathogenicity for laboratory animals—*Br melitensis* readily causes infection in monkeys, but not always in guinea-pigs, whereas *Br suis* is very virulent in the latter, *Br abortus* is very variable in its pathogenicity, but falls between the other two species in its pathogenicity in guinea-pigs.

Distribution in the body—secreta and excreta—The organisms are present in the blood during the fever. They occur in large numbers in the spleen, from where they can be recovered during life by spleen puncture, or after death. They occur in the urine in about 10 per cent of cases, and the urinary infection may persist for some months. They have been isolated from human milk. They can also be demonstrated in the faeces by a special technique.

Portals of entry—The usual means of infection is by the gastrointestinal tract but the organisms can also enter with comparative ease through the conjunctival, nasal, or naso-pharyngeal mucous membranes, and also through the skin, but in the latter case entry is probably effected through small abrasions. Laboratory infections are very common, and recently in the United States 57 laboratory infections were reported from 17 laboratories. The persistence of the infection in the British army and navy in Malta even after all consumption of goat's milk had been stopped, the higher incidence in the dry dusty season the ability of the causal

organisms to resist drying, and the fact that goats pass them in their urine, all suggest the possibility that entry through the nasal and respiratory mucous membranes may play an important, though secondary, part in the epidemiology of the disease.



Figure 112: Schema showing the origin media and mode of transmission and route of entry of the infecting organisms in Malta fever.

Differentiation of *Brucella* species—There are two antigenic elements present in different proportions in the three allied organisms, the antigenic structures are shown diagrammatically in figure 113.

Thus, the organisms cannot be separated by straight agglutination, but *Br melitensis* can be separated from the *abortus-suis* group by absorption of agglutinins. The brucellæ can also be differentiated by means of their growth in the presence of certain dyes, the following table, which is taken



*melitensis* *suis* *abortus*

Figure 113: Diagram indicating the proportions of the antigenic elements M and A in the three recognized species of *Brucella*.



with minor modifications from Topley and Wilson (1936), summarizes the means of differentiation —

Type	Usual habitat	Grown in absence of extra CO <sub>2</sub>	Growth in presence of				H <sub>2</sub> S formation	Anti-genically
			Basic fuchsin 1 in 25 000	Thionin 1 in 50 000	Methyl violet 1 in 100 000	Pyronin 1 in 200 000		
<i>melitensis</i>	Goats sheep	+	+	+	+	+	—	<i>melitensis</i>
<i>abortus</i>	Cows horses	—	+	—	+	+	+	<i>abortus</i>
American suis	Dogs	+	—	+	—	—	+	<i>abortus</i>
Danish suis	Pigs	+	—	+	—	—	—	<i>abortus</i>

**Immunity** — One attack does not appear to confer complete immunity against a subsequent attack but the second attack will be mild

The fact that the organisms circulate in the blood for a number of days does not suggest the early formation of immune bodies, agglutinins usually appear, but they may be of low titre and are not constantly present

No satisfactory immunity can be produced by inoculation of dead cultures

#### PATHOLOGY

Most have been a few deaths a clouds the true picture

The spleen is nearly always enlarged it is soft and hyperæmic Occasionally there are small hæmorrhages and infarcts

Histologically the sinuses are dilated there is proliferation of the reticulo endothelial cells, and a hyperplasia of the lymphoid tissue

There is often slight enlargement of all the lymphatic glands but especially those of the mesentery In the intestines there is sometimes slight congestion of a few Peyer's patches but there is neither ulceration nor even any other constant changes in the intestinal lymphoid tissue

The sigmoidoscope sometimes shows a granular colitis This causes a watery diarrhoea that appears to respond to specific vaccine therapy

**Blood picture** — There is usually anæmia and this tends to be progressive red cell counts are sometimes below 3 000 000 but seldom if ever below 2 000 000 per cmm in an uncomplicated case There is a slight tendency towards a leucopenia but this is neither marked nor constant, however the count in an uncomplicated case is never above 10 000 per cmm and sometimes as low as 4 000 per cmm The differential count is more characteristic the lymphocyte count often amounts to 50 per cent of the total and there is a fairly constant large mononuclear increase an actual granulopenia

As noted above brucellæ can be isolated from the urine in about 10 per cent of samples

## SYMPTOMATOLOGY

The incubation period is from 10 to 15 days the extremes being from 11 to 17 days as a general rule but in exceptional cases it may extend to 40 days.

There are mild prodromal symptoms malaise and headache followed by a slow onset of fever increasing in a situde and inability to concentrate pains all over the body and particularly in the joints pains in the eyes on lateral movement anorexia insomnia and irritability The fever in a case stop ladder a as n t phed and reaches 102° or 103°F in 6

non inflammatory hydrarthrosis of the painful joints. Mild abdominal symptoms may develop congestion and discomfort usually with constipation but occasionally with watery diarrhoea the tongue is very furred. The pulse is soft rapid and irregular. Bronchial symptoms are common. The spleen may in time become enlarged it is usually soft and tender. There is increasing toxæmia in severe cases but in the average case the patient does not feel particularly ill finds bed irksome and is very irritable.

The fever reaches its highest point in about a week. It remains as a high remittent or continuous temperature for possibly another week and then step ladders down reaching normal usually within three weeks. It

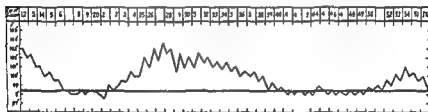


Figure 114 Temperature chart of a case of Malta fever (or erg)

joint pains are the rule

Other symptoms are orchitis or mastitis neuritis *eg* facial and intercostal neuralgia sciatica and lumbago and more rarely temporary paralysis. Sometimes there is blurring of the vision and vertigo. In the long continued cases loss of weight and even emaciation will be an important symptom.

In severe cases there may be purpuric spots oozing from the mucous membranes and even profuse bleeding into the stomach intestine or bladder.

tuberculosis. The usual lung complication is bronchitis but broncho pneumonia is not uncommon. Other complications are parotitis suppurative orchitis and arthritis pregnant women usually abort.

with minor modifications from Topley and Wilson (1936), summarizes the means of differentiation —

Type	Usual habitat	Grown in absence of extra CO <sub>2</sub>	GROWTH IN PRESENCE OF				H <sub>2</sub> S formation	Anti-genically
			Basic fuchsin 1 in 25 000	Thionin 1 in 50 000	Methyl violet 1 in 100 000	Pyronin 1 in 200 000		
<i>melitensis abortus</i>	Goats sheep Cows horses	+	+	+	+	+	—	<i>melitensis abortus</i>
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Danish suis	Pigs	+	—	+	—	—	—	<i>abortus abortus</i>

**Immunity**—One attack does not appear to confer complete immunity against a subsequent attack, but the second attack will be mild.

The fact that the organisms circulate in the blood for a number of days does not suggest the early formation of immune bodies, agglutinins usually appear, but they may be of low titre and are not constantly present.

No satisfactory immunity can be produced by inoculation of dead cultures.

#### PATHOLOGY

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The spleen is nearly always enlarged, it is soft and hyperæmic. Occasionally, there are small hæmorrhages and infarcts.

Histologically, the sinuses are dilated, there is proliferation of the reticulo-endothelial cells, and a hyperplasia of the lymphoid tissue.

There is often slight enlargement of all the lymphatic glands but especially those of the mesentery. In the intestines, there is sometimes slight congestion of a few Peyer's patches, but there is neither ulceration, the intestinal lymphoid tissue  
as a granular colitis. This causes

a watery diarrhoea that appears to

**Blood picture.**—There is usually progressive red cell counts are sometimes below 2,000,000 per cmm in an tendency towards leucopenia, but this is neither marked nor constant, however, the count in an uncomplicated case is never above 10 000 per cmm and sometimes as low as 4,000 per cmm. The differential count is more characteristic, the lymphocyte count often amounts to 50 per cent of the total leucocytes, and there is a fairly constant large mononuclear increase,

As noted above, brucellæ can be isolated from the urine in about 10 per cent of samples.

## SYMPTOMATOLOGY

The incubation period is from 10 to 15 days, the extremes being from 4 to 17 days, as a general rule, but in exceptional cases it may extend to 40 days.

There are mild prodromal symptoms, malaise and headache, followed by a slow onset of fever, increasing lassitude and inability to concentrate, pains all over the body and particularly in the joints, pains in the eyes on lateral movement, anorexia, insomnia, and irritability. The fever increases in ladder-like steps, reaching  $102^{\circ}$  or  $103^{\circ}\text{F}$ . in five

non-inflammatory hydrarthrosis of the painful joints. Mild abdominal symptoms may develop, congestion and discomfort usually with constipation, but occasionally with watery diarrhoea, the tongue is very furred. The pulse is soft, rapid, and irregular. Bronchial symptoms are common. The spleen may in time become enlarged, it is usually soft and tender. There is increasing toxæmia in severe cases, but in the average case the patient does not feel particularly ill, finds bed irksome and is very irritable.

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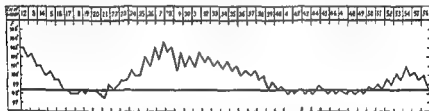


Figure 114: Temperature chart of a case of Malta fever (orig)

may remain normal for a day or two and then it starts to rise again. The waves are not usually regular but on the average they maintain about a three week periodicity. With the relapse of the fever, the symptoms tend to return but not usually in such a severe form though sweating and fleeting joint pains are the rule.

Other symptoms are orchitis or mastitis, neuritis, e.g. facial and intercostal neuralgia sciatica, and lumbago and more rarely temporary paralyses. Sometimes there is blurring of the vision and vertigo. In the long continued cases, loss of weight and even emaciation will be an important symptom.

In severe cases there may be purpuric spots, oozing from the mucous membranes, and even profuse bleeding into the stomach, intestine, or bladder.

... .. purpose in patient to pulmonary tuberculosis. The usual lung complication is bronchitis but bronchopneumonia is not uncommon. Other complications are parotitis, suppurative orchitis, and arthritis, pregnant women usually abort.

**Clinical types**—As in most other diseases, the individual's response to the infection will vary. The following clinical types can be recognized:—

(i) *The mild*—In this type there is only a single bout of fever lasting perhaps a fortnight, or a mild bout and one short relapse.

(ii) *The classical*—The attack of moderate severity, as described above, with repeated relapses lasting several months.

(iii) *The chronic*—The disease may start as an ordinary or mild of any acute febrile attack, and there is little sign of the usual joint pains and sweating occur. In this type the patient is ill for months without of the usual

marked toxæmia, and a relapse-like course.

### DIAGNOSIS

**Discussion**—It is justifiable to make a provisional diagnosis on clinical grounds, and in certain circumstances it may be permissible to maintain it without confirmation from the laboratory, but, obviously, confirmation should be obtained whenever possible.

With proper laboratory facilities, it should be possible to isolate the causal organism in half to three-quarters of the cases seen early in the disease. Of those first coming under observation and relied upon. Of these, the agglutination test should certainly be done. If the agglutination test is negative, and the opsono-cytophagic test may be used as the third or as a confirmatory method.

**A Clinical.**—The principal points are—high fever with little prostration.

The urinary culture is said to be positive at some stage of the disease in 75 per cent of cases, but the general experience is that 10 per cent of specimens of urine will give a positive culture, the statements are not incompatible.

**C Specific antibody tests**—(1) **Agglutination**—This is considered the most reliable of the specific tests, other than the isolation of the causal organism.

organism, in most cases the agglutinins appear in the blood between the fifth and tenth days, and remain for a long but variable time for many years in some cases and for one year in the majority. Agglutinins are not, however, constantly present even in the acute stages of the disease, and

should be expected

The agglutination test is not species specific, and there is usually no significant difference between the titres obtained with *Br melitensis* and *Br abortus* emulsions, but, after the minor agglutinin (see figure 113) has been absorbed, agglutination will occur with the specific antigen with

in this test is to prepare or 'Brucellergin', as prepared by Huddleston (1934), is probably the best, but if neither this nor any other standardized preparation is obtainable, one can be made from a heat-killed fat-free bacillary emulsion. Reactions are apt to be sharp and there may even be constitutional symptoms, so that a 1-in-100 dilution of the standardized 'brucellergin' should be used first, and later, if a negative result is obtained, a 1-in-10 dilution.

## occurs

A negative result may occur as early as the 7th day of the disease.

Outline of technique and interpretation of results—To 5 ccm of blood, 0.2 ccm of 20 per cent sodium citrate is added. A bacillary emulsion of 6 000 million organisms (or equivalent to a suspension of 300 parts per million of suba) in normal saline is made. One cubic centimetre of each of these two is mixed in a test tube which is put into an incubator at 37°C for one hour, the sedimented on clean slides these are dried rapidly, smear is fixed and stained. The slide the number of polymorphonuclears that

The expected result is as follows—

Differential diagnosis—The disease may simulate any of the long-continued fevers of temperate or tropical climates.

The cosmopolitan diseases include—tuberculosis, especially of the lungs and intestinal tracts, the enteric fevers, rheumatic fever and rheumatism, *Bacillus coli* infections, and the Pel-Ebstein syndrome in Hodgkin's disease.

Amongst tropical diseases, kala-azar is the most likely to lead to confusion, there are many points of similarity the long continued undulant fever, the bouts of fever are usually of short duration, but this is usually more pronounced in kala-azar than in undulant fever, and the slow establishment of debility, and the granulopenia—which again is more marked in kala-azar than in undulant fever. Untreated malignant tertian or relapsing benign tertian malaria, and amoebic hepatitis with abscess formation may simulate Malta fever, but in both these diseases the therapeutic test should clear up matters, and in liver abscess there is usually a leucocytosis.

### PREVENTION

The following are the three main lines along which attempts at prevention should be made —

(i) The elimination of the source of infection primarily in goats, sheep and cattle.

(ii) The prohibition of the use as food or the sterilization of the medium of infection.

(iii) The protection of susceptible and exposed persons e.g. by education and if necessary regulation and by inoculation.

(i) *The elimination of the source of infection*—The destruction of the

has not proved very successful, but this is a matter for further veterinary research.

It is probably very seldom that an infected person is a serious source of infection, but bacteria may be passed in the excreta is a preventive measure.

*Food, or the sterilization, of the medium of infection*—The prohibition of the consumption of milk or milk products, or the enforcement of pasteurization will be successful only if the consumption of infected milk is the sole or main means by which infection is acquired. Even in Malta there is some doubt on this point, though prohibition of the use of goat's milk and goat's milk products by army and navy personnel appeared to be completely successful for some years. In other places, e.g. the south of France, where the disease occurs mainly amongst dairy workers, there are obviously other channels of infection.

Pasteurization will kill the brucellæ, and if this procedure can be enforced, this means of spread of the disease will be effectively controlled.

(iii) *Protection of susceptible and exposed persons*—Dairy and other workers should be warned to wash their hands before taking food, and to keep their hands free from abrasions.

It is also to be noted that inoculation with killed cultures of brucellæ is very disappointing. More work before this measure can be recommended as a routine.

### TREATMENT

*Discussion*—The state of the treatment of Malta fever is at present far from satisfactory. The introduction of the sulphonamide preparations raised hopes that a specific might be found for this infection, and many enthusiastic reports appeared in the medical press, these early reports were soon followed by cautionary, and eventually by frankly condemnatory

ones. As a new chemotherapeutic drug appears almost monthly it is impossible to keep up to date and it would be foolish to be dogmatic on this subject and to discuss them all, further one hopes that some day a specific of this nature will be found. Meanwhile it will be necessary to use successful methods.

Even here it is not possible to include a wide range of clinical states. In the best of cases, except in bed and careful nursing, eating will necessitate frequent

pains will require local applications; and in the later stages massage to the wasted limbs will be helpful.

After a severe febrile bout the patient should be kept in bed for four or five days after the temperature has fallen to normal especially in a cold or temperate climate where chills are likely later when the disease enters on its more chronic stages it will usually not be possible to maintain this routine and it is questionable if it is necessary to limit activities except during the febrile attacks. (Some writers recommend long continued confinement to bed to a certain extent in the clinical course cases would have to be proved. It does not seem to be advocated.)

The diet should be as liberal as possible but naturally during the acute stage it will have to be modified.

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For  
now

In acute toxæmic cases a pint of 5 per cent glucose may be given intravenously every day this will combat dehydration assist detoxication and provide nourishment.

**Vaccine therapy**—On the whole vaccine therapy seems to have produced the best results especially in chronic cases. The aim should be to

should determine the next

Vaccines should not be given during the high febrile stages nor when toxæmia is marked and in these stages serum therapy is indicated.



**Serum therapy.**—This should be used only in the acute and toxic stage to 1 or 5

of 50 saline

beer

when joint pains are troublesome, good results have been claimed, particularly in relieving some of the tiresome symptoms

**Chemotherapy.**—Dyes have been used for some time with varying results. Some success has been claimed for acriflavine, a maximum dose of 10 milligrammes per kilogramme body-weight, i.e. 0.7 gramme for the average adult, was given intravenously

Trypaflavin has also been used, 10 ccm of a 1 per cent solution is given intravenously, once a week. A special precaution is that patients must be kept in a darkened room, as during this treatment they become very sensitive to light. Good results have been claimed with these dyes, but their administration is not entirely without risk

Many of the new 'sulpha-' preparations have been tried, but so far, as stated above, without any uniform success. The writer has used sulphapyridine and sulphathiazole, without very convincing results. The chart of one case recently treated is shown (figure 115), it seems possible

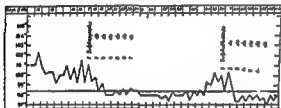


Figure 115 Temperature chart in Malta fever. Sulphapyridine appeared to control the fever, but a relapse occurred which again appeared to respond to sulphathiazole

that the sulphathiazole controlled the fever, but our experience here is that a spontaneous cure often occurs after one or two bouts. Recent reports on sulphapyridine suggest that the history of the early reports on sulphonamide (*vide supra*) is being repeated. The writer has seen no reports on treatment with sulphadiazine

Neither sulphanilyl-guanidine nor succinyl sulphathiazole, which are so useful in the dysenteries, is likely to be useful in this disease on account of their low absorption

### PROGNOSIS

The average duration of the illness in frank clinical cases is at least two months, but durations up to two years have been reported. The death rate amongst such cases is from 2 to 5 per cent

three

### ABORTUS FEVER

**Discussion.**—As abortus fever is so closely related to Malta fever, only the points of distinction will be dealt with here

(or *Br abortus* var *suis*) are the cultural differences and in the table on page 356

*Br abortus* and *Br suis* cause enzootic infections in cattle and pigs,

investigated that can claim freedom from this infection

Epidemic features — Infection is transmitted from cattle and pigs to man in a number of ways, which are best shown diagrammatically, see figure 116 below

Abortus fever has an even more definite occupational distribution than Malta fever and is very prevalent amongst meat packers who handle pig carcasses amongst stockyard workers butchers, and veterinarians as well as amongst farm and dairy workers



Figure 116

### SYMPTOMATOLOGY

On the whole, the disease tends to run a much more benign course than Malta fever, this applies particularly to *Br abortus* infections. The vast majority of cases are (i) mild and (ii) types are rare but are enzootic

commonest symptoms are malaise headache sweating, a marked tendency to lassitude and fatigue, vague body pains, rigors, constipation and anorexia, more or less in that order of frequency, from 100 per cent down to about 60 per cent, in frank cases. The spleen is sometimes enlarged but less frequently than in Malta

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*Br suis* infections are on the whole much more severe than *Br abortus* infections, *Br abortus* infections acquired in the laboratory seem to be much more severe than those acquired naturally. All *Br suis* infections and laboratory infections with *Br abortus* are nearly always acquired through the skin or mucous membranes whereas natural *Br abortus* infections are acquired *via* the gastro intestinal tract. It seems possible therefore that the route of invasion has some effect on the severity of the infection.

The *prognosis* is distinctly better in *Br abortus* infections than in Malta fever and *Br suis* comes between the two.

#### DIAGNOSIS

Und  
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to this infection can be taken advantage of, and guinea pig inoculation should be added to the bacteriological methods

\* estrated blood should  
be sediment from the  
sk or groin  
ad on the guinea pigs  
and from the organs

particularly the spleen smears and cultures are made

*Br abortus* infection in milk can usually be detected only by animal inoculation. 2 to 5 ccm of separated cream is injected into each groin

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# MELIOIDOSIS

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**Definition** —Meloidosis is a fatal disease of protean symptomatology, caused by a glanders like bacillus *Pfeifferella whitmorei* (*pseudo mallei*) which is transmitted to man sporadically from rats amongst which it is epizootic in certain eastern tropical countries

**Discussion** —The excuse for the inclusion in this book of a disease of which only about a hundred cases have been reported in the 30 years since it was first described, is that there are reasons to believe that it is much more widespread than our present knowledge appears to indicate

**Historical** —Whitmore and Krishnaswami (1912) described a disease that they

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## ÆTIOLOGY

In most laboratory animals, they produce a fatal septicæmia as well as a local abscess when injected. In the guinea-pig a small dose given intraperitoneally will cause a painful swelling of the testicles in two days (Straus's reaction), a large dose will kill the animal before this reaction has had time to occur.

Infection of animals will also occur after oral administration. The organisms are excreted in the faeces and urine of infected animals.

In man, it produces a septicæmia and/or a pyæmia, and can be recovered from most tissues of the body after death.

Transmission takes place mainly by the oral route, it is believed, by contamination of food by rat's faeces and/or urine.

#### EPIDEMIOLOGY

agents or persons of the  
association with rats

#### PATHOLOGY

The essential pathological lesion is a nodular focus similar to milium  
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inal fluid  
confined  
o amœbic

#### SYMPTOMATOLOGY

Very few cases have been diagnosed ante mortem, and in these the symptomatology has shown wide variations. The earliest reported cases had cholera-like symptoms—a watery diarrhoea, vomiting and collapse with death within two or three days, other cases have shown pneumonia-like symptoms and death has been postponed by several days, and in yet others a pyæmic condition has been reported, with subcutaneous abscesses or even a cutaneous eruption simulating smallpox. In this last group, the patients usually survive for two or three weeks, in some cases death has occurred after two months, and two patients have eventually recovered.

with such a varied  
al diagnosis presents  
laboratory medium  
ic abscesses. Where  
material should be  
mea-pig, this latter  
l taken from decom-

A dilution of 1 in  
3,000 was reported in the blood of one surviving patient. This method  
may prove of use for making a diagnosis in less acute cases.

**Prevention and treatment** —In our present state of knowledge, no preventive measures other than the destruction of rats and the protection of food from contamination by these rodents can be advocated

**Treatment** is entirely symptomatic. Obviously, the new chemotherapeutic agents should be given a trial

**Prognosis** —Only two patients have been known to survive

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## THE INTESTINAL FLUXES

**Introduction**—The treatment of fever and the intestinal fluxes forms at least 90 per cent of the daily routine of the practitioner in the tropics, in malarious districts, fever will probably claim the greater share of his attention, but even here the fluxes will come a close second, in other districts they will be an easy first. The causes of diarrhoea are numerous away from the intestinal flux, but in the tropics nearly every organ in the body may be the seat of an unimportant symptom, such as gonorrhoea, syphilis, and tuberculosis. The causes of dysentery are well defined aetiology, such as bacterial (amoebic disease), and mechanical (obstruction of the bowels). The intestinal flux which will produce the most important forms of

intestinal flux that have some special association with the tropics, most of these have a specific and recognized aetiology

### CLASSIFICATION AND DEFINITIONS

**A Cholera**—An acute specific diarrhoea caused by *Vibrio cholera*, in which the small intestine is mainly involved

**B Dysentery**—A clinical condition in which frequent stools containing blood and mucus are passed, with tormina and tenesmus. Aetiologicaly, dysentery can be placed under a number of headings—

#### I Caused by bacteria

(i) **Shiga dysentery**—A very severe dysenteric condition, always acute in its early stages, caused by *Bacterium dysenteriae* Shiga

(ii) **Flexner group dysentery**—A dysenteric condition, sometimes severe, and usually acute in its early stages, caused by a group of organisms of the type *Bacterium dysenteriae* Flexner

(iii) **Sonne type dysentery**—A dysenteric condition, usually of a milder type, caused by *Bacterium dysenteriae* Sonne

(iv) **Salmonella group dysentery**—A dysenteric condition, usually followed by dysenteric symptoms, associated with infections of the *Salmonella* group, *Salmonella paratyphosus* B, *enteritidis*, and *typhimurium*

#### II Caused by animal parasites

(a) **Protozoal dysentery** (i) **Amoebic dysentery**—Primarily a dysenteric condition usually with an insidious but occasionally an acute onset, caused by *Amoeba dysenteriae*

(ii) **Ciliate dysentery**—A mild but serious dysenteric condition caused by *Balantidium coli*, a ciliate common in pigs

(iv) **Coccidiosis**—A rare diarrhoeal or dysenteric condition caused by *Isospora hominis*

(v) **Malarial dysentery**—A dysenteric condition associated with an intense *Plasmodium falciparum* infection

Leishmanial dysentery is often included under this heading, but the evidence is against there being any such specific condition. In experimental animals, and to a less extent in man, the mucous membrane of the intestine is often heavily infiltrated by leishmanæ, but histologically there is no tendency towards ulceration. The ulceration that occurs as a complication, often a terminal one, is due to some other infection, and/or to malnutrition.

(b) **Metazoal dysentery** (s) **Bilharzial dysentery**—A dysenteric condition caused by the eggs of helminths of the genus *Schistosoma* (*Bilharzia*)

(u) **Other helminthic dysenteries**.—Diarrhoeal and dysenteric conditions caused by helminths of the genera *Ceaphagostomum*, *Heterophyes*, *Fasciolopsis*, and *Strongyloides*

(c) **Viral dysentery**.—In *lymphopathia venereum*, proctitis which may develop into a severe ulcerative condition of the rectum or sigmoid often occurs. This ulcerative condition is usually above a stricture but it may follow or precede stricture formation.

C **Chronic ulcerative colitis**—A chronic non-specific ulcerative condition of the colon that is very frequently the sequel to one or other of the acute specific dysenteric conditions classified above. This is a condition that is well known in temperate countries but is far more common in the tropics.

#### D *Diarrhoeal diseases that are probably dietetic in origin*

(i) **Sprue**—A disease of disordered metabolism in which the passage of frequent frothy and fatty stools is a very prominent symptom, usually occurring in Europeans living in a tropical country, under abnormal dietetic conditions.

(ii) **Para-sprue**—A diarrhoeal disease due to multiple often self-imposed, dietary deficiencies associated with anaemia and disordered carbohydrate metabolism, and common amongst residents—indigenous and otherwise—of tropical countries but not peculiar to them.

(iii) **Other nutritional diarrhoeas**—Diarrhoeas that are important but not the main symptom of other nutritional diseases e.g. pellagra (qv).

#### E *Diarrhoeas of special environmental conditions*

(1) **Hill diarrhoea**—A disease of mixed ætiology but possibly associated with the atmospheric conditions at high altitudes.

(ii) **'Gippy tummy' and allied conditions**—A diarrhoeal condition, probably mainly of bacterial origin, precipitated by local chilling occurring in dry tropical and sub-tropical countries (e.g. Egypt) where there is a high diurnal range of temperature. (No further reference will be made to this condition, about which there has been much correspondence in the medical press recently; the general opinion is that it is usually caused by one of the recognized dysentery organisms and precipitated by sudden chilling.)



# CHOLERA

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September 1830 from there it spread to Leningrad (June 1831) Berlin (August) Hamburg (October) and thence across the North Sea to Sunderland in Great Britain and it reached Edinburgh in June 1832. Later it crossed to America

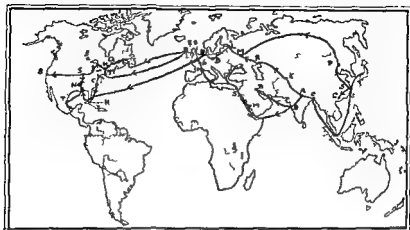


Figure 116a. Routes taken by cholera two pandemics starting from Calcutta (C) in 1817 and 1842

A	Astrakan	1830	July 20	1847	June
M	Moscow		Sept		Sept
L	Leningrad	1831	June 16	1848	June
B	Berlin		Aug 01		
H	Hamburg		October		Sept
■	Sunderland		Oct 24		Oct 4
E	Edinburgh	1832	Jan 23		October
Q	Quebec		Apr 1		
N Y	New York		June		Nov 9
N O	New Orleans	1833	Jan		Dec 8

1865 pandemic starting from Hindu Kumbh mela reached Bombay then to Mecca by Mohammedan pilgrims

B	Bombay	1865	Apr 1
M	Mecca		May
■	Suez		May
M	Marseilles		July
P	Paris		July
E	England		August

N Y New York 1866 May

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enforced and which control the spread not only of cholera but of many other

even in a scientific world ripe for the acceptance of any new bacteriological discovery. Some of the bacteriologists of the day seemed to think that Koch had displayed rather bad taste in introducing a curved organism where they had expected a straight one. His theory however soon received general credence and the matter was left where it stood for some years. The application of the agglutination test and Pfeiffer's phenomenon at first seemed likely to clarify the

In this confused atmosphere the Health Organization of the League of Nations constituted a cholera commission and the Indian Research Fund Association decided to devote a considerable sum to cholera investigations. Bacteriological investigations at the Standards Laboratory at Oxford (Gardener and Venkatraman 1935) and the National Institute of Medical Research at Hampstead with the collaboration of field workers in India have led to a considerable clarification of the position as it stands to-day (*vide infra*).

# ÆTIOLOGY

have a common H antigen but a number of O antigens that divide this group into many sub groups. The important one is O sub group I which includes the true non hæmolytic cholera vibrio and the hæmolytic El Tor vibrio. Of the true cholera vibrios there are two sub types 'Inaba' and 'Ogawa'.

Thus the true cholera vibrio is a non hæmolytic vibrio that is agglu-

cholera

*The cholera vibrio*. Morphology and cultural characteristics — *Vibrio cholera* is a motile comma shaped organism 1.5 to 4  $\mu$  long by 0.2 to 0.4  $\mu$  in thickness with a single polar flagellum staining easily with weak carbol fuchsin gram negative and growing easily on ordinary bacteriological media at 37°C (*see plate B*).

On agar plates the colonies are round 1 to 2 mm in diameter low convex translucent greyish yellow with a smooth or finely granular glistening surface and entire edge of amorphous or finely granular structure of the consistency of butter and easily emulsifiable. On horse-blood agar plates after 24 hours at 37°C there is an abundant growth and the colonies are surrounded by a 2 mm zone of hæmolysis, there is however no true

The cholera vibrio

" " " "

... non-haemolytic cholera vibrios

By carrying out these three tests, strong, though still presumptive, evidence is obtained regarding the identity of the vibrio.

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type I, and will give

reaction, and if it do

a true cholera vibrio

**Resistance**—The cholera vibrio has no resistant phase, it survives on clothes from one to three days in a moderately moist atmosphere, but is easily killed by drying. It dies in sewage within 24 hours. In pure water it dies rapidly, but in some 'potable' waters it will survive for a considerable time.

For the survival and multiplication of the cholera vibrio, salt and organic matter are necessary in the water, the higher the concentration of the former the lower need the latter be, and *vice versa*. The limits for multiplication are 1 per cent salt (sea salt) with 1 in 500,000 peptone, and 0.1 per cent salt with 1 in 500 peptone, for survival the range is distinctly wider, for example vibrios will survive for some weeks in 0.02 per cent salt and 1 in 5,000,000 peptone. The hydrogen-ion concentration limits are pH 6.0 and pH 9.4.

Many natural

lent to 1 in 5,000 to

per cent

It is killed at 55°C in 15 minutes, in 0.5 per cent phenol in a few minutes, and in 1 in 500,000 water.

**Bacteriophage**

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Personal susceptibility also plays an important part, Macnamara reported an incident in which 19 persons ate a meal heavily contaminated by a cholera stool and only 5 developed classical cholera. An incident

\* **Cholera-red reaction** Ten cubic centimetres of peptone broth (peptone—1 per cent, sodium chloride—0.5 per cent in distilled water, adjusted to pH 8.0) is

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happened in the writer's personal experience when cholera infection was introduced into the children's ward of a hospital, in so-called skimmed milk—probably milk diluted with dirty water—that he had ordered for a child with infantile cirrhosis of the liver. There were six children in the ward, two died of cholera, two had a mild diarrhoea, and two had no symptoms at all. From the stools of all six patients, cholera vibrios were isolated.

**Toxins.**—This is always a controversial point. The general opinion is that there is no true soluble exotoxin secreted, but that there is an exotoxin which is adsorbed to the cell wall. It is possible to produce an exotoxin *in vitro*, it may do so *in vivo*.

**Distribution in the body.**—The vibrios are confined almost entirely to the small intestine and the appendix, and they are usually found in the duodenum and the jejunum. They do not penetrate the biliary passages and are isolated from pneumonic patches in the lungs.

**Mode of escape from the body.**—Vibrios escape from the body in the stools and in the vomitus, but recent investigations have shown that they cannot be isolated from the urine if measures are taken to avoid faecal contamination of the urine (Chatterjee and Malik, 1938). The patient does not usually pass true cholera vibrios in the stools for more than five days from the time of first infection, this is also true in the sub-clinical (or contact) case of cholera infection. In a few instances, 'carriers' have been detected who passed cholera vibrios up to two weeks but it is very doubtful if there is a true carrier state in cholera as there is in typhoid (Taylor, 1941); in this connection, reports previous to 1935 must be discounted, on account of the doubt that exists regarding the true identity of the organisms passed. The human source of cholera infection is thus cases and contacts (sub-clinical cases).

acidity

**Media of infection.**—The commonest medium of infection is water. Other fluids also, particularly milk, will carry the infection. Uncooked foods and any food allowed to remain uncovered are common media of infection, especially during an epidemic, e.g. fruit and vegetables which may have been sprinkled with water taken from any wayside source, to keep them fresh, food exposed for sale in the open bazaar and by itinerant sweetmeat vendors, and left exposed.

**Active agents.**—Probably the most important factor in the spread of the disease is the rat, should not be considered as a source of morbid material.

**Immunity.**—There is evidence that, in man, some—though possibly not complete—natural immunity exists. It has been claimed that new-



It should be appreciated that in any particular year the incidence of cholera in an epidemic area may far exceed that in the endemic area from which the infection originated

The origin and maintenance of infection — Cholera is an eminently preventable disease because as far as is known the origin of infection is invariably a human being. Although the alliterative

trinity, the case, the contact and the carrier is always mentioned, the tenets of belief of the sanitarian they are not in fact three but one source for the contact is a sub clinical case of cholera, the carrier is only a prolonged one. There is no known animal source of infection and the true vibrio has not been isolated from any natural source. The absence of cholera for more than a few weeks

The maintenance of the infection in the endemic areas has interested bacteriologists and epidemiologists. Survival and multiplication in village water supplies for many weeks is possible (*vide supra*). The present opinion is that there is no other residual source of infection in endemic areas except cases and that infection is maintained by case to case passage of virulent non haemolytic O sub group I vibrios. The vast majority of the villages in the endemic areas are of the most primitive nature: there are no latrines and no protected water supply. The people use the open fields and frequently the banks of (reservoirs) for defaecating. Open tanks are their only water supply. They will bathe in the tanks, wash out their mouths and even drink water at the same time.

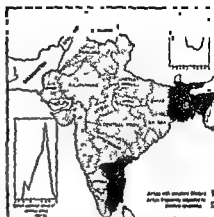


Figure 117

a week or so

In India — With the very great increase in facilities for travel, the chances of spread of cholera from the endemic areas to other parts of India are considerable, but it has been found that normal railway travel on business or pleasure does not tend to spread the disease to an



that, though the sanitary arrangements are far from perfect, especially the small stations, there are latrines and a safe water supply. Such travelling, even the poorest are seldom usually indicates that the

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poor, and such money and food as they have when they leave their homes are soon finished, so that they arrive in an ill-nourished and exhausted state. Further, it is difficult to make satisfactory sanitary arrangements for the literal millions that attend some of these *melas*, e.g. the Kumbh mela at Hardwar, at which the attendance has been estimated at over a million on certain days. Those pilgrims who travel through such areas widely amongst other pilgrims with them, and, returning to

As recently as 1930, an epidemic of the United and Central Provinces

India has in recent years been almost entirely by the sea routes, and with improved port sanitation and has been largely controlled. Her

infection being carried back to the countries would be considerable unless special precautions were taken

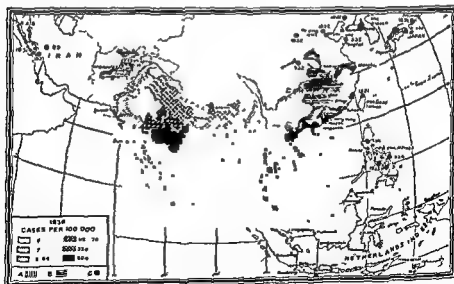


Figure 118 Geographical distribution of Cholera in Asia, 1930-1938 (League of Nations Weekly Epidemiological Record)

- A Disease reported in 1937 ■ Disease reported in 1938  
C The dates shown on the map for the various territories correspond to those of the latest occurrence of the disease

**Climate and cholera**—The importance of climate in determining cholera endemicity is obvious from the similarity of the climates in all the

ture appears to be less important in this respect for cholera spreads rapidly in cold countries. Attempts to delimit the endemic areas on climatic criteria alone have not been entirely successful. Rogers' criterion of an absolute humidity of 0.400 inches of vapour pressure throughout the year can be accepted only in that this constant high humidity is a common feature of all the true endemic areas but it is not correct to suggest that all areas with this degree of humidity are endemic areas even in India.

**Seasonal incidence**—The factors that determine this are different in the endemic and epidemic areas.

In the endemic areas temperature and absolute humidity are the main

obviously some other factor also comes into operation for cholera incidence declines. This other factor is probably the mechanical flushing of contaminated water supplies and the alteration in their chemical and physical character. Cholera incidence shows a rise in October as the monsoon subsides and it falls again at the end of the year when temperature and both relative and absolute humidity fall.

In the epidemic areas on the other hand the cholera incidence curve follows the absolute humidity curve throughout the year reaching its peak in the monsoon months July to October (figure 117).

**Variations from year to year forecasts**—In both the endemic and

by an epidemic in the next year and after two such successive failures an epidemic is even more certain.

The importance to the local sanitary staff of knowing what the chances are of cholera occurring in the epidemic areas or of the incidence being abnormally high in the endemic areas is obvious and has led to a very serious study being made of the cyclical incidence of cholera and of the climatic and other factors that influence it. A number of methods of forecasting have been devised but on the whole Rogers (1933) method has

sub endemic areas in Bengal. The subject however is too technical to be

undertaken by the average practitioner, as well as being outside his sphere (Russell, 1925, Lal, Raja and Swaroop, 1941)

**The natural subsidence of an epidemic**—This may be due to the favourable climate, to some change in the water-supply, the exhaustion of one water-supply or the cause, or to the exhaustion of the clinical material. It has also been claimed that it is effected by the development of bacteriophage in the water supply.

Towards the end of an epidemic there is usually a decrease in the severity of the disease and a lowering of the mortality.

**Race, sex, and age distribution**—There appears to be little difference in the susceptibilities of the different racial elements in the population and, even in the highly endemic areas, the indigenous inhabitants are very susceptible. Men are said to be more frequently affected than women, but it seems possible that there has been a selective tendency in the data on which the statement is based. There are also relatively fewer children than adults amongst hospital patients admitted with cholera, but children are susceptible, and in them the disease will usually run a severe course, an infant aged two months with cholera was recently admitted to a Calcutta hospital.

## PATHOLOGY

**Pathogenesis.**—The vibrios do not invade the tissues, and do not apparently produce any exotoxin. The endotoxin that results from the death and destruction of the great outpouring

the tissues and blood. The tissue changes observed are usually attributed to the absorption of this toxin, but could probably be explained by the dehydration of the tissues themselves and by the hæmo concentration and low blood pressure which results in temporary ischæmia.

**Morbid anatomy.**—The body is dehydrated, though usually well nourished as the illness is a short one. There is marked early post-mortem rigidity, in some cases the stiffening of the limbs is almost ante-mortem. The muscles are dehydrated, dark red, and firm, and show curious post-mortem contractions which in some cases are so marked that they have been known to cause a body to fall off the post-mortem table.

In the abdominal cavity the omentum will be found as a sticky curled-up mass, the serosa, especially of the stomach, duodenum and small intestine, are pink, the lymph follicles are slightly enlarged, and the contents of the bowel are the typical rice watery alkaline fluid in which there are flakes of mucus and sometimes streaks of blood. The mucous membrane of the stomach, the small intestine and often the large intestine are congested and there may be petechial hæmorrhages.

The liver is congested and full of dark viscid blood, there may be some toxic degenerative changes in the parenchyma cells, especially if death took place in the later stages. The gall-bladder is full and the viscid bile will not pass along the ducts even when the gall bladder is squeezed. The spleen is usually small and contracted. The pericardium often shows petechial hæmorrhages, the right heart and the large veins are full of dark tarry blood. The lungs are usually shrunken and anæmic, but, if death occurs in the later stages especially when the intravenous saline therapy has failed, they may be œdematous.

haemorrhage  
with a  
microscopical  
examination

The kidney changes are more in the nature of a nephrosis than a nephritis and

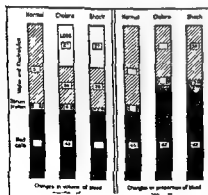
changes in any of the organs and in others in one or two organs only the most constant changes are those due to dehydration

**The blood**—On account of the dehydration there is often a polycythæmia the red cell count not infrequently rising to 7,000,000 per cmm or more. There is a disproportionate leucocytosis often up to 20,000 per cmm with a relative large mononuclear increase. The red cell volume percentage which is normally 45 to 48 may rise to 55.

The sedimentation rate is increased in the majority of cases but not markedly. It would appear that there are two opposing influences because it is mainly in the serious cases in which the specific gravity of the blood is high that the sedimentation rate is within normal limits (deMonte and Gupta 1941).

With the suppression of urine the non protein nitrogen and urea are raised considerably but it returns to normal comparatively rapidly usually within a week after the urinary flow has started again.

**Dehydration**—In the severe case of cholera the symptoms are mainly due to dehydration and loss of chlorides and alkalis (*vide supra*). The similarity between a patient with cholera and one in shock



the specific gravity of the blood the

dom higher

**Renal failure**—It is easy to understand how haemoconcentration circulatory failure through loss of blood volume and some degree of toxic vaso-

The urine—The urine, prior to suppression, will be highly coloured

content may be as low as 0.1%. This quantity, and its urea content very low concentrate urea. During the next few days efficiency of kidney function more urine may rise above normal. Subsequently output will increase further and the urea percentage again drop.

### SYMPTOMATOLOGY

Instances of cholera in which contact carriers are important (vide supra). From a clinical point of view cholera infection may produce any one of three types of cholera—

- (a) *Mild*—choleraic diarrhoea
- (b) *Typical severe cholera* with purging and vomiting
- (c) *Cholera sicca*, a comparatively rare, very severe form of cholera in which the toxæmia is extreme, causing paralysis of the bowels so that the patient dies within a few hours after some vomiting but no diarrhoea, the bowels are found distended with rice-watery fluid laden with vibrios.

within 24 hours

The onset may be with a moderate diarrhoea which develops in severity but it is much more frequently sudden with violent purging and vomiting. After the lower bowel has been emptied of faecal matter at the first few purgings the stool takes on the typical rice-water appearance—a non-offensive whitish fluid with flakes of mucus and occasionally streaks of blood. The diarrhoea is profuse and painless—described alliteratively as pints of pale fluid painlessly pouring away. The diarrhoea is shortly followed by profuse watery vomiting. This constitutes the first stage, or stage of copious evacuations, and its duration will vary inversely with the severity of the symptoms.

The patient then passes into the second stage, the stage of collapse. The purging and vomiting continues the former becoming a continuous process and the latter being uncontrolled and often precipitate. The classical cholera facies are assumed—the eyes sunken and cheeks hollow, the skin cold and clammy to the touch and cyanotic, the fingers shrivelled (washer woman's fingers), the voice husky, and the expression anxious, the patient complains of extreme thirst, and becomes very restless, the blood pressure falls and the pulse cannot be felt at the wrist, the surface temperature may be as low as 95°F, the rectal temperature at the same time may however

slowly recover. But if the algid stage continues for long the stage of

reaction' may be as serious as the earlier stages. The usual explanation of this reaction is that the recovery of the circulation means more blood flowing through the intestinal blood vessels, and more absorption of toxins. However, if the kidney failure has been long continued and/or there has

start to flow again, and a  
ases the temperature rises  
*Cholera* has been described  
suppressed in the collapse  
and doubts whether the

early rise of temperature that may occur is really part of the cholera syndrome. He has seldom seen any febrile reaction in an uncomplicated case that could not be accounted for by the infusion of pyrogen containing saline. The charts of ten consecutive cases are shown in figure 120, in one case the rectal temperature was high on admission, but in no case was there any reaction rise. Later rises in severe cases are more easily explained.

Death may occur in this stage from toxæmia, azotæmia, hyperpyrexia, or from one of the various complications that may appear (*vide infra*). Anuria will usually result in death within four or five days, but there have been instances in which the patient has passed into a semi-comatose state and died on the 9th day of the anuria, recovery has been reported after anuria for four days.

The recovery may be temporarily accompanied by the passage of a little concentrated urine with a high percentage of albumin and many hyaline and granular casts, when the blood pressure falls again, the

patient will once more become anuric. When, however, the patient passes as much as two pints of clear urine in 24 hours, the danger of relapse has usually passed. The toxæmia of cholera appears to be comparable to that following ischæmia in crush injury when blood again flows through the injured limb.

Convalescence is usually comparatively rapid, but great care should be exercised, as sudden heart failure as the result of slight exertion is not uncommon.

**Complications.**—Enteritis and diarrhoea, pneumonia, parotitis, slough-

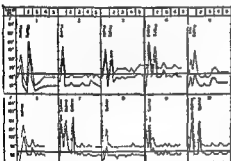


Figure 120 Temperature charts of ten consecutive cases of cholera (broken line = rectal temperature)

free water

## DIAGNOSIS

In the large majority of cases, and especially during an epidemic, it will be possible to make a clinical diagnosis with a considerable degree of certainty. In fact, during an epidemic, all suspected cases should be treated as cholera, and all contacts as potential cases of cholera and as probable

cases of vibrio infection. The diagnosis of the isolated case is more important from a public health point of view than from the patient's for when there is severe purging and vomiting with consequent dehydration the intravenous saline treatment is indicated whatever the aetiology.

Even without full laboratory facilities, a provisional bacteriological diagnosis can be made by examining wet and dry films under the microscope. The latter is made by taking a shred of mucus from the stool, making a smear on a slide, and staining with weak carbol fuchsin. In the wet film the large number of the organisms, their uniform character, and their very rapid rotatory movements, will lead one to suspect cholera. In the stained film the characteristic comma shaped vibrios and their 'fish in a stream' arrangement will add to the suspicion.

Whenever possible the diagnosis should be confirmed by the following bacteriological procedures—

- (i) Inoculate several loopfuls of stool into a tube of peptone water (1% peptone 0.5% NaCl adjusted to pH 8.4) incubate for 8 hours take a loopful from the surface and examine fresh and stained. If they are gram negative motile vibrios—
- (ii) Take a loopful from the peptone culture and streak on (a) Vedder and Van Dam (haemoglobin peptone glycerin and KOH—pH 8.4) (b) Dieudonne or (c) Aronson plates and incubate for 12 hours. Pick out greenish (in a and b) or red (in c) colonies and examine to confirm that they are vibrios.
- (iii) Carry out a slide agglutination test with standard high titre anti O sub-group I cholera serum to exclude all but the El Tor and the true cholera vibrio.
- (iv) In order to show whether hæmolytic (El Tor) or nonhæmolytic (true cholera vibrio) to a 5% sheep-blood corpuscular suspension in saline add an equal quantity of vibrio emulsion incubate at 37° C and read after two hours and again after 8 hours.

**Differential diagnosis**—Cholera will have to be distinguished from, amongst others the following conditions—

(a) *Fulminant bacillary dysentery*, the diagnosis will be bacteriological but it is unnecessary to wait for this, as intravenous saline treatment is indicated in either case, though in a case of Shiga dysentery the early administration of anti serum would probably improve the prognosis.

(b) *The algid and choleraic forms of malaria* the differential diagnosis here is very important for though the administration of intravenous saline would do the malaria patient no harm and probably some good the withholding of specific anti malarial treatment might easily be fatal, if there is any doubt a blood film should be examined immediately.

(c) *Trichinosis* the acute gastro intestinal onset of a heavy infection of *Trichinella spiralis* may simulate cholera and later the muscular cramps might be a confusing element. The exclusion of this diagnosis will be difficult and a positive diagnosis of cholera must be sought. This infection however is rare in India, the main home of cholera.

(d) *Food poisoning*—staphylococcal or streptococcal mushroom etc.

(e) *Arsenic or antimony*

The distinguishing features of the last two are shown in the table following—

TABLE VI (*Differential diagnosis of cholera*)

	Cholera	Food poisoning	Arsenic (and antimony) Poisoning
<i>Epidemiology</i>	Associated with other cases in neighbourhood	Often single group of persons who shared meal no secondary cases	Often one person only
<i>Incubation</i>	24-72 hours	4-24 hours	1-2 hours
<i>Onset</i>	With purging	With vomiting	With burning in throat followed by vomiting
<i>Nausea and retching</i>	None	Yes	Yes retching marked
<i>Vomiting</i>	Precipitate watery rarely blood Continuous	Often single severe vomit mucus blood streaked	Violent continuous mucus often freely streaked with blood
<i>Evacuation</i>	Early Continuous pouring out of pints of watery fluid inoffensive	Frequent Usually follows vomiting faecal plus blood and mucus often offensive	Delayed Single massive followed by frequent passing blood and mucus
<i>Tenesmus</i>	None	Yes	Very marked
<i>Abdominal tenderness</i>	None	Marked All over abdomen	Very marked
<i>Dehydration</i>	Very marked	Distinct	Slight
<i>Muscular cramps</i>	Constant and severe	Less constant Extremities only	Severe
<i>Surface temperature</i>	Subnormal	Often up to 100-102°F	Normal or subnormal
<i>Headache</i>	None	Often	Often
<i>Urine</i>	Suppressed	Seldom suppressed	Sometimes suppressed later
<i>Blood</i>	Leucocytosis mononuclear increase	Normal	Slight leucocytosis Normal differential

## PREVENTION

**Grand strategy**—No cholera pandemic has occurred since 1884 and in fact for the last thirty years the disease has been confined to its Asiatic homes and to other Asiatic countries in their immediate vicinity. This



in this country with a view to stamping out the disease in the endemic areas

In 1931, the Indian Research Fund Association made cholera one of their main subjects of research, with some of the results reported above. The Indian workers, in collaboration with others in England, established the identity of the true cholera vibrio, showed that the cholera case was the only source of infection, and defined the true endemic areas in India, thereby they opened the way for a definite policy of control. This policy,

provinces in which the endemic areas exist

**Prevention of epidemic extension**—In all countries there are strict regulations at ports, and certain measures taken vary in accordance with the local conditions. In India, measures taken have gone as far as to provide for anal swabs being taken from all the lower-class passengers.

Within countries, control measures are more difficult to carry out, and have on the whole been less successful, but during the last few decades special efforts have been made to prevent epidemic extension as a result of religious melas. At the sites of these melas, latrine arrangements, anti-fly measures and protected water supplies have been instituted. Provision has been made for the immediate treating and isolation of the sick. Similar measures have been made at various points on the roads and railways. During the last few years, systematic disinfection of the villages at the height of the epidemic seasons, and measures for detaining and treating persons showing suspicious symptoms in any village where a case has been reported, have been undertaken. Disinfection of the water supplies in the whole community undertaken.

Attempts are also made to control the movement of the population to prevent extension of the epidemic to other villages.

In the matter of disinfecting wells, discrimination should be observed and only suspected sources of infection treated at first, for, if all well water is made undrinkable, the inhabitants will be compelled to find other waters which may be even more contaminated. Under *infra* chlorination of water supplies.

**Control in the endemic areas**—Here the public health policy to be followed is different. One of the main differences is that the disease is of a permanent nature, and occurs throughout the whole year. In these areas, the population should be provided with a protected water supply. Cholera could be stamped out if the habit of indiscriminate

(see footnote on water supplies\*)

\*Water supply in the water table is an ideal. Although greater quantities of water are nearly all part of the 150 feet deep,

depth of the course being 100 feet. The water of the wells is 30 to 40 feet deep and varies as it is

defecation in the open fields around the village that is general in most Indian villages probably helps to spread infection during exacerbations of

because though it may prevent the full development of symptoms, it is unlikely to preclude infection completely such an infection which will result in the passage of virulent vibrios for a few days by an unsuspected individual is a greater source of danger than a frank case of cholera

allowed to take any food on the premises or to smoke flies should be excluded rigidly from the wards and latrines and all those who come in contact with cholera patients should be inoculated preferably a week or

be used unless it is known to have been made from boiled water and no cut fruit or food cooked the previous night and left standing should be eaten These are the standard rules to avoid bowel disease They should always be

necessary for the well strainer to be in a sand stratum which is below the water-table height during the dry season The water although hard is usually of high purity

Open wells have a greater yield than shallow tube wells in that they also serve as a reservoir However it is harder to maintain purity even when the wells are protected by a proper apron and parapet wall The purity can be maintained if the well is covered and a pump installed

When the water supply is from a *doba* or stream it must be pumped into a reservoir where proper disinfection can be carried out

There is still a mistaken idea of the danger of sub-soil pollution of a well Nearly all well pollution is from the surface In a limestone formation or where there are fissured rock formations pollution may travel quite long distances but in other formations the extension of pollution from a source depends upon the texture of the soil the height of the water table the slope of the water table and the direction of the flow

The old theory that the water in a well is pure is a

rare case United the director little c planning a latrine it should be below the well The direction of the ground water flow can be roughly estimated by the topography of the ground

followed in the tropics but they must be observed with religious formality during a cholera epidemic. There is little danger of direct infection of personal attendants on the sick, provided that they avoid a precipitate vomitus splashing into their faces and never take food on the premises or until they have changed their clothes and washed their hands.

### Special measures of prevention

**Inoculation**—Haffkine, who was a student of Pasteur, carried out experiments in Paris in 1892 and applied them in India. He used live avirulent cultures followed by virulent cultures. Kolle showed that killed cultures were equally efficacious, and killed cultures have been used since. Cholera vaccine has been used very widely for a quarter of a century. Recent evidence of its value rests mainly on one statistically designed and executed investigation conducted under the auspices of the Indian Research Fund Association (Russell, 1927). The figures were as follows—

	Persons	Cases	Deaths
Two doses of vaccine by injection	8 485	31	11
Three doses of oral vaccine	4 982	18	4
Controls	40,258	711	277

It is usual to give two doses, but in many wholesale inoculation schemes it has only been practicable to give one, and the results have not been much inferior. This fact, and the apparent equal success of the oral vaccine, about which many workers are very doubtful, has led the sceptics to question the value of cholera vaccine altogether.

The vaccine should be prepared from recently isolated strains of non-hæmolytic O sub group-I cholera vibrios. The vaccine should be formalin-killed and contain 4 000 million organisms per c.c.m. in 0.5% phenol, the usual dose is 1 c.c.m. followed a week later by a second dose of 2 c.c.m.

Immunity is said to last from 3 to 6 months, and there does not appear to be a negative phase.

**Oral vaccine**—Besredka's oral bilivaccine has been used more extensively in cholera than any other vaccine. It was first investigated by Russell (*loc. cit.*)

results

**Disinfection of water supplies**—**Chlorination**—For filtered water supplies, the usual rule is one part in five million, that is one part of chlorine, or if the chlorine content of 3 parts of bleaching powder, this is two parts per million gallons of water. But, as the chlorine fixing power of powder varies from sample to sample and as the chlorine fixing power of different water supplies also varies, no rule of thumb can be adopted and the amount to be added must be calculated for each well or cistern.

The following is a standard method of calculating the amount of bleaching powder to be added.

Three standard solutions made with distilled water are necessary:

- (a) 1 in 1 000 solution of the bleaching powder to be used
- (b) 10 per cent potassium iodide solution
- (c) 1 per cent starch solution

The volume of water to be chlorinated must first be ascertained. For wells this can be calculated from the depth of the water and the diameter of the well by the formula  $\pi r^2 \times \text{depth}$  where  $r$  is the radius (half the diameter) of the well. The capacity of tanks and cisterns is calculated by multiplying the length

by the breadth by the depth of the water One cubic foot of water is equivalent to 7.48 gallons

*Example* A well = 10 feet deep and has a diameter of 6 feet  
Therefore it contains  $\pi \times 3^2 \times 10 \times 7.48 = 3.14 \times 9 \times 10 \times 7.48 = 1768$  gallons

Take five white bowls or flasks and in each place 500 ccm of water to be treated

Stir the mixture in each bowl with a clean glass rod beginning with the bowl containing the least amount of chlorine solution and going to the one containing the next smallest and so on

Allow them to stand for at least an hour Then test for free chlorine by adding to each bowl about 1 cc of freshly prepared starch gives a faint blue colour Note

added  
of po  
figure  
the u  
the a  
alread

then  $\frac{1768 \times (18 + 3)}{1000000}$   
= 0.037128 lb  
= 260 grains (or about 17 grammes)

solutions

The calculation is made as follows

Minimum number of drops of bleaching powder solution added to the first bowl in which the blue colour was distinct

Number of drops from the dropper that make a drachm  $\times 0.44 + 0.021 =$  Grains per gallon of water to be treated

*Example* If the fourth bowl was the first to give the blue colour then  
 $4 \times 0.44 + 0.021 = 0.1585$  grains per gallon  
= 158 grains per 1000 gallons  
or in the case of the example given above  
 $1000 \times 158 = 158000$  grains (or about 18 grammes)

present A dilution of 1 in 500 000 which produces a faint purple colour in filtered water kills cholera vibrios in a very short time but it will not kill all coliform organisms even in 24 hours

This dilution is obtained by adding  $\frac{1}{500}$ th grain of permanganate to each gallon of water or roughly one pound to each 50 000 gallons

In our hypothetical well which contained 1768 gallons the amount of permanganate required would be a little over half an ounce

Neither the permanganate nor the bleaching powder should be thrown into the well, but should be mixed in a bucket, the supernatant fluid being

poured off and renewed until the whole amount has gone into solution. Then, the water in the well should be thoroughly mixed by repeatedly lowering and raising the bucket.

### TREATMENT

**Historical**—Charms, amulets and magic were credited with playing important parts in the treatment of cholera. . . . till held their ties. This is employed by the were scarcely it appears to 1 to 2 grains was more utrous acids

quinine, strychnine, arsenic, iron, and in fact almost every drug in the pharmacopœia, and many that were not in it. The multiplicity of drugs suggests very strongly that none was of any real value. Other methods employed were venesection, blistering, cupping, wrapping in cold sheets, hot baths, 'electro-magnetic insulation', and a number of other procedures.

With the advent of bacteriology and Koch's discovery of the vibrio, the intestinal antiseptics naturally had a phase, but the value of none was established.

Saline injections were used nearly a hundred years ago in England. The immediate result was said usually to be good, but as emphasis is laid on the word *immediate*, one must assume that the final results were disappointing and

better understood and more promptly put into operation.

**Introduction**—Treatment must be considered under three headings:—

*A. Specific*

*B. Maintenance of biochemical equilibrium*

*C. Symptomatic*

Hitherto the failure of specific treatment has led to an emphasis on the other two aspects of treatment. The complete success of efficient biochemical-maintenance treatment in a large percentage of cases indicates that, even in those cases in which the natural immunity fails to prevent the establishment of infection, immunity is rapidly developed and soon over-

**A. Specific treatment**—There are two objectives—

(1) The destruction of the vibrio—All the various intestinal antiseptics that have been used in the past have failed to influence the course of the disease in the case of cholera.

The advocates of bacteriophage have claimed an earlier disappearance

atment,  
mouth  
cholera,  
every

two hours, or large doses at longer intervals for at least two days.

The essential-oils mixture that has been advocated by some workers is presumably supposed to act as a disinfectant. The essential-oils mixture consists of:—

R. Olei caryophylli	}	m℥i
"  caryoputi		
juniperi		
Acidi sulphurici dil		℥℥ss
Spiritus ætheris		℥℥ss

Half a drachm of the mixture is given in an ounce of water every 15 minutes, up to a maximum of 16 doses

sixty cases in which this dosage was given, we have lost no case against a death rate of about 11 per cent amongst patients treated with saline infusions only (Napier *et al* in press). Reports from elsewhere have not been so satisfactory.

(ii) The neutralization of the toxin.—No great success has been achieved in this direction. Potassium permanganate has been most disappointing in the writer's experience and, in the large doses advocated, it appears to cause gastro-intestinal irritation very frequently. It seems very questionable whether its *in vitro* toxin-oxidizing properties are reproduced *in vivo*. The dose recommended is two enteric coated pills of 2 grains each — 15 — at — for the first twelve hours and then one half

are —

(i) the replacement of fluid

(ii) the maintenance of the blood and tissue chlorides at their normal level, and

(iii) the counteraction of acidosis

All three can be achieved by suitable intravenous therapy, for example, by the hypertonic and alkaline saline treatment recommended by Rogers. The procedure that he suggested was as follows —

Rogers' treatment—Two solutions are prepared —

(a) the hypertonic saline consisting of

(b) the alkaline saline which is prepared as follows —

sodium chloride—90 grains  
pure or distilled water 1 pint

this solution is autoclaved to ensure sterility, and to it is added, from a previously sterilized packet containing the exact amount, 160 grains of bicarbonate of soda\*

\* Sodium bicarbonate is converted to carbonate if a solution of it is heated for any length of time

He took as his main indication for the giving of intravenous saline the specific gravity of the blood, measured by means of glycerine bottles (*vide supra*). A specific gravity of 1061 he suggested indicated a loss of one pint of fluid, 1062 two pints 1063 three pints and so on. Fluid was replaced accordingly, by giving first one pint of alkaline saline and making up the balance with hypertonic saline. He recommended giving the intravenous salines at the rate of about a pint in 5 minutes.

Rogers' treatment has been the basis of all successful treatments of cholera for the last 25 years. During this time many modifications have been introduced and individual workers have naturally interpreted his technique in different ways.

**Modified procedure**—In the cholera wards of the Campbell Hospital in Calcutta the procedure is as given below, this scheme has been worked out by the physicians especially Dr B C Chatterjee, attached to this hospital in conjunction with the cholera research workers at the Calcutta School of Tropical Medicine. The following four solutions are made up and kept ready for use. They are made with pyrogen-free\* sterile distilled water, and the precautions suggested above regarding the sterilization of bicarbonate in the dry state are observed.

(a) <i>Hypertonic saline</i>			
Sodium chloride	140 grains or 16.00 grammes		
Pyrogen free distilled water	1 pint		1 litre
(b) <i>Alkaline saline</i>			
Sodium chloride	90 grains or 9.00 grammes		
Sodium bicarbonate	180 grains	20.50	
Pyrogen free distilled water	1 pint		1 litre
(c) <i>Alkaline hypotonic saline</i>			
Sodium chloride	60 grains or 6.80 grammes		
Sodium bicarbonate	180	20.50	
Pyrogen free distilled water	1 pint		1 litre
(d) <i>Bicarbonate solution (5 per cent)</i>			
Sodium bicarbonate	440 grains or 50.00 grammes		
Pyrogen free distilled water	1 pint		1 litre

**Indications**—Intravenous solutions are given in all severe cases in which there is any evidence of dehydration or if the patient is at all collapsed, if possible, the extent of this dehydration and collapse are

are found in  
Subsequent  
prepared as

In a clean glass still re-distil some freshly distilled water to which a little sulphuric acid and one or two crystals of potassium permanganate have been added to give it a faint pink colour. If during the process of distillation the pink colour disappears from the water in the still a little more sulphuric acid and potassium

is been previously prepared  
and sulphuric acid then  
pyrogen free water and finally

sterilized by autoclaving

The pyrogen free water is sterilized in an autoclave and may be used for about 3 to 4 days

When distilled water is already available the following method may be adopted to ensure that it is pyrogen free

Add powdered charcoal (BDH activated charcoal for preference) to distilled water. This is shaken thoroughly for a few days to settle out the supernatant fluid in a clean flask or bottle (*vide supra*) with cotton wool but closed with a glass stopper and the neck of the receptacle, it must be stored for a few days treated again

ascertained by estimating the specific gravity of the blood and taking the blood pressure. If 80 mm of mercury, or the specific gravity is 1.050 to 1.052, two pints are prescribed, if 1.060 to 1.062, two and a half, up to three pints. It is seldom wise to give more than three pints in the first instance, at any rate in the low-weight type of Indian, but, if circumstances permit, the perfusion should be continued by the drip-feed method.

**Method**—The specific gravity of the blood is estimated under clinical conditions by adding drops of blood to a series of bottles of glycerine diluted with distilled water to make the specific gravities 1.050 1.052 1.054 and so on up to 1.070, for practical purposes, it is usually sufficient to have bottles from 1.054 to 1.064. If the specific gravity of the blood is greater than that of the glycerine in the bottle, the drop will sink; if it is less, it will come to the surface. The bottles can be used for some time if they are carefully corked; if they are not, the glycerine will evaporate and the specific gravity will rise as a result.

right's pipette  
in the bottle of  
glycerine will probably  
be led drop either  
if the specific gravity of  
the blood is less than  
that of the glycerine or  
less than as between

FIGURE 119

FIGURE 121

that is, from 24 to 48 hours from the onset of the disease, and 1 part of hypertonic saline to 4 parts of distilled water. After 48 hours the most prominent feature, and hypotonic alkaline saline should be given. If however the specific gravity of the blood is not much increased but nevertheless the patient is suffering from acidosis, then the bicarbonate solution only is required, and about half a pint of this should be given.

It will very often be necessary to repeat the infusions, sometimes as many as half a dozen times, if the fluid evacuation continues or if the patient collapses again, or if the dehydration is re-established (evidenced by a rise in the blood

in  
the  
reser-

cedure of running in two pints of hypertonic saline and following this by a pint of plasma to keep it there, so to speak, has been adopted in a few cases, apparently with complete success, but, as it will be seen from figure 119, there are not the same indications for giving plasma in cholera as in shock.



Figure 121 Apparatus for giving saline, with the drip-feed apparatus incorporated in the tube (in this figure the length of the tubing between the drip-feed and the needle is shorter than it would be in practice)

ratus may be interposed a foot below the reservoir,



and 3 inches of glass tubing to act as a 'window' a short way from the lower end. At the lower end of the tube, a record needle adapter, preferably with a stop-cock, is inserted, and a serum syringe needle fitted (see figure 121) for giving by the open method the needle is fitted (see figure 121) For cannula, again preferably

A suitable vein, usually in front of the internal ma

of the  
comp  
elbow

align with the body in  
pad placed under the

A sphygmomanometer cuff or a tourniquet is applied to the arm, compression of the deeper arterial supply is avoided, if necessary, the patient should be made to open and close the hand or to bend and extend the elbow, several times in order to fill the veins

The selected area is painted with tincture of iodine and then washed with alcohol. Local anaesthesia of the skin may be produced by injecting a few drops

with a fine hypodermic  
it be held firmly so

d with the infusion  
expelled. The needle  
ery acute angle with  
into the vein. Some  
be experienced hand  
a sudden failure of  
about or just below  
ned, blood will flow

into the tube and be visible at the window. The tourniquet is now released and the reservoir raised and the flow will be reversed. The reservoir should be attached to a stand, about 3 to 4 feet above the level of the patient.

A very convenient refinement is a serum syringe with a side nozzle to which the lower end of the tubing from the reservoir is attached, the adapter being discarded, the needle is attached in the usual position. With the aid of this syringe the operator has perfect control of the needle whilst inserting it into the vein. The piston is slowly withdrawn when blood will appear. The tourniquet is released and the side stop-cock opened to allow the saline to flow.

When the veins are collapsed the open method is employed. A tourniquet is applied as before. Under a local anaesthetic a small incision is made the skin being steadied by the index finger and thumb of the left hand. The vein is isolated by forceps dissection. The closed forceps or an aneurysm needle are then passed under the vein and a double strand of sterilized catgut is drawn

under it. The catgut is divided to provide two ligatures. The distal piece is drawn down under the exposed vein and is tied the ends being left long. The proximal one is drawn up under the vein to the upper end of the wound.

The fluid is now allowed to flow through the cannula until the vein is filled.

The vein being  
fine scissors  
knotted and is  
then started

When the infusion is completed the cannula is withdrawn but the ligature not knotted as it is a later time when it is needed.

used again

**Rate and temperature of administration**—At first, while the patient is pulseless, the infusion can be given briskly, at about 4 ounces per minute,

\* As bicarbonate solution will cause pain and a sharp local reaction if even a small amount is allowed into the subcutaneous tissues a small amount of isotonic saline should always be placed in the reservoir first, until the cannula is in situ and a satisfactory flow has started.

be met by reducing the rate of flow rather than by abandoning the procedure. After three pints have been given, the infusion may be continued at a very much slower rate—40 or even 20 drops per minute (1 pint in four or eight hours).

If the rectal temperature is  $101^{\circ}\text{F}$  or above, all intravenous infusions reaction possibly ending in hyper-  
temperature of the fluid must certainly

If the rectal temperature is also  
e saline up to body temperature

weather in most endemic areas this

is a very unnecessary complication of administration

**Other routes of administration**—In children and when it is not possible to find a vein, hypertonic saline may be administered subcutaneously, intramuscularly, into the sternum or tibia or into the peritoneal cavity, alkaline saline cannot be given by these routes. In mild cases alkaline isotonic saline can be given per rectum but if there is much purging little will be absorbed. After administration of salines intraperitoneally the foot of the bed must be raised as the absorption from the pelvic peritoneum is very poor.

**C. Symptomatic treatment**—The intravenous therapy will play an all-important part in the treatment and prevention of collapse and of many other serious complications such as anuria but other measures may also have to be adopted.

**Collapse and shock**—The administration of atropine sulphate  $1/75\text{th}$  grain when the patient is first seen to be repeated after about 12 hours if the patient is still collapsed was first suggested by Lauder Brunton and is recommended by Rogers. Atropine reduces all secretions, except renal secretion it therefore helps to conserve fluid and at the same time to reduce the tendency to oedema of the lung when saline is given. It also reduces irregular peristalsis, and is a cardiac stimulant. This appears to have some effect in reducing the shock. Pitressin 1 c cm (pituitary extract—posterior lobe) or, if not available, desoxycorticosterone acetate 20 c cm (synthetic suprarenal cortical extract) will often help towards the recovery of the pulse during the collapse stage. Other routine measures for the treatment of shock, hot water bottles, massage, etc. may have to be resorted to.

**Anuria**—With the recovery of the blood pressure the kidneys will usually start to secrete urine again but if hypertonic saline, alkaline saline, bicarbonate solution, and injection of pitressin and desoxycorticosterone acetate fail, glucose 5 per cent (1 pint), intravenously, strophanthin gr  $1/100$ , caffeine and sodium benzoate gr  $\frac{1}{2}$  intramuscularly, hot fomentations to the loins, dry cupping, hot colonic washes, intravenous sodium sulphate (1.89 per cent) by the drip-feed method and finally distension of the bladder with warm citrate saline (2 per cent citrate in normal saline) should

In the treatment of cholera

very

ould be treated

often

uring, this will

of calomel repeated at half-hour intervals up to six doses, followed by a dose of bismuth salicylate. The following prescription will be found useful —

R Calomel	gr 1
Chloretone	gr 2
Menthol	gr 1
Sodium bicarbonate	gr 2½

Muscular cramps should respond to the hypertonic saline treatment, but, if they persist and are very painful, self-administered whiffs of chloroform will often meet the case.

Morphia and alcohol should be avoided at all stages of the disease. Rogers considered that the early administration of morphia definitely affected the later prognosis, making both suppression and acidosis much more likely to occur.

Emu

flavo

water

stomach or the rectum, it should be given intravenously as a 5 per cent solution, up to a pint.

Later, arrowroot, albumin water, milk whey, milk, fruit juices, meat

so, the patient may be allowed to return to a full diet

save the patient from exhaus-

great care must be taken not to allow

as sudden heart failure is not uncom-

valence is very rapid, once the acute symptoms have subsided.

**Summary of treatment** — The fate of the patient will depend on the skill of the physician, on the facilities that the latter has at his disposal, and on the energy that he devotes to the case. Of the 'specific' treatment

given. The symptomatic treatment must be given as the condition of the patient indicates. Convalescence should not be hurried.

**Some reported results** — In 1936 Pasricha, deMonte and O Flynn carried out a large series of treatments to appraise the value of cholera-phage in the treatment of cholera, the crude results were as follows —

	Treated with phage	Treated without phage
Total number of cases	684	635
Total deaths	92	114
Percentage mortality	13.5	16.6

Further analysis of the data suggested that the difference between the phage treated cases and the others was greater than the crude figures indicated.

In a second series three years later Pasricha deMonte Chatterjee and Mian (1939) compared a number of forms of treatment. After excluding all patients who died within three hours of admission and the very old and very young the results were as follows —

Treatment	Number of patients	Number of deaths	Percentage mortality
Calomel	75	9	12.0
Potassium permanganate	35	4	10.8
Essential oils	46	4	8.7
Sulphapyridine	43	4	9.3
Cholera phage	43	1	2.3
	244	22	9.0

In this series the phage was prepared by a different method. The cases were taken strictly in rotation but by a mistake two patients were put on calomel to each one put on each of the other treatments.

In 1941 Chopra deMonte Gupta and Chatterjee reported the results of treatment with small doses of sulphanilic guanidine as follows —

	Number of patients	Number of deaths	Percentage mortality
Sulphanilic guanidine	468	26	5.56
Controls	87	6	6.90

coverly rate was higher with the large dosage.

**Conclusion** — In all these series all the patients were subjected to the routine saline infusion treatment. The results appear to indicate that cholera phage has a definite beneficial effect. They also indicate a progressive improvement in the routine treatment for cholera in the hospital in which this was carried out or possibly a decrease in the virulence of the disease; there is little external evidence to support the latter interpretation.

#### PROGNOSIS

This is intimately associated with treatment and the reader is referred to the previous paragraphs.

sub-ideal hospital conditions at the present day, it is seldom above 10 per cent. It must be remembered that results of treatment in hospital will *always* be better than in the 'field', because, in the worst cases death occurs before the patient can reach hospital, and therefore not only are conditions better, but the population is a selected one. In cholera epidemics it is usually found that the death rate is much higher at the beginning than at the end of the epidemic.

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# BACILLARY DYSENTERY

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and adult diarrhoea in temperate countries

(iv) Other rarer organisms, e.g. *Bacterium ambiguum* Schmitz, and organisms of doubtful pathogenicity, e.g. *Proteus morganii*, *Bacterium alkalescens*

table VII

Resistance.—Dysentery bacilli are killed at a temperature of 55°C in one hour, by 0.5 per cent phenol in 6 hours, and by 1 per cent phenol in 17 hours. They survive in wa-  
ive for  
- days

TABLE VII

Shows sugar reactions of dysentery bacilli (after Topley and Wilson, 1936)

	Glucose	Mannitol	Lactose	Saccharose	Dulcitol	Rhamnose	Sorbitol	Lactus milk	Indole
<i>Bact. dysenteriae</i> Shiga	A	—	—	—	—	—	—	sl A	—
<i>Bact. ambiguum</i> Schmitz	A	—	—	—	—	A	A ±	sl A	+
Newcastle bacillus	A g	A (g)	—	—	A (g)	—	—	sl A sl alk	—
<i>Bact. dysenteriae</i> Fletner	A	A	—	A ±	—	A ±	A ±	sl A sl alk	±
<i>Bact. sonnei</i>	A	A	(A)	(A)	—	A	A	A (clot)	—
<i>Bact. alkalescens</i>	A	A	—	—	A	A	A	alk	+
<i>Proteus morganii</i>	A	—	—	—	—	.	.	N alk	+

A = acid  
alk = alkaline  
g = a little gas

± = sometimes  
± = usually  
■ = slight  
Brackets indicate late formation

All are non motile except *Proteus morganii* and possibly the Newcastle bacillus  
all reduce nitrates to nitrites and are Voges Proskauer negative

Toxins: The only dysentery organism that is a toxin producer is the Shiga toxin-producing *E. coli*.

group and Sonne bacilli injected into laboratory animals are toxic, but only in much larger doses (about 20 times) than in the case of the Shiga organism. They do not give rise to very efficient antitoxic sera.

Distribution in the body and the recovery of the organism.—The

only 5 per cent during the third five days. With the new media now in use, much higher percentages should be obtained. The organisms are never isolated from the blood or urine.

Carriers.—It is not uncommon for a patient to continue to pass dysentery bacilli for a considerable time after the acute symptoms have subsided. In one large scale investigation during the 1914-18 war, it was shown that 7.59 per cent of patients became carriers and that 2.78 per cent were 'persistent' carriers, that is, they continued to pass bacilli for three months or more in the carrier state regularly, whereas for two or three passing bacilli for a transient

New media (*vide infra*) for the isolation of dysentery bacilli have thrown new light on the carrier problem, particularly with regard to the symptomless (or contact) carrier. It has been shown that ratio of carriers is on the average 1 to 3 in the case of Flexner infections.

Shiga toxin is the sole cause of

European countries are usually traced to a carrier employed in the preparation of food but in the tropics while flies are probably the commonest agents of infection, a number of epidemics have been traced to unsatisfactory water supplies.

Routes of invasion.—Invasion is always by the oral route. As in cholera, low gastric acidity probably helps to allow the bacilli to pass through the stomach and invade the bowel.





## PATHOLOGY

**Morbid anatomy**—Except that in the acute toxic cases there is marked congestion of the solid organs, especially the liver, kidneys and suprarenals in which there may be some toxic necrosis of the parenchyma cells, the lesions are confined entirely to the large bowel, the ileo-cæcal valve, and the last few feet of the small intestine beyond congestion there is usually little evidence of the disease on the peritoneal surface of the intestine, except possibly in the chronic ulcerative stage where there may

be severe focal infection, the following pictures may be encountered (i) In a very severe case where the toxæmia was intense and death occurred early, the whole or a greater part of the large intestine and lower end of the ileum is lined with a white or yellow (bile-tinged), fibrinous membrane, suggestive of a diphtheritic membrane (ii) When death occurs at a slightly later stage in an acute attack, the mucous membrane is intensely red, and is covered by strips of dark greenish-grey necrosed mucous membrane, that are separating particularly along the tops of the ridges of the mucous membrane. It is possible, if great care is exercised to see the

on account of the congestion and œdema of the surrounding mucous membrane. The ulcers are usually but not always transverse they are irregularly

but it shows a tendency to heal. The condition is well seen by means of

cases come to the post-mortem table but this condition can be seen with the sigmoidoscope

**Sites of the lesions**—In severe attacks the whole extent of the large bowel and the last few feet of ileum are involved, however, the majority

tion and thickening of the mucous membrane, with œdema polymorpho-nuclear infiltration, minute hæmorrhages, and a considerable amount of

mucus and sometimes a little fibrinous exudation. In the severer forms, there is an extension of the inflammatory processes to the submucosa, where the lymph follicles are the most important centres of inflammatory activity. There is in these cases considerable thickening of both the mucous and submucous layers, the inflammatory oedema leads to thrombosis of the veins with numerous hæmorrhages in the submucosa, and coagulation necrosis causes the death and separation of the mucous membrane. There is sometimes a certain amount of round-celled infiltration of the superficial muscular layers, but the deeper layers and the serous coat are practically never involved. With the loss of the mucous membrane, there is formation of new blood vessels, columnar epithelial ulcer. During the inflammatory processes, even if the mucosa is not destroyed altogether, there is a considerable amount of

normal bowel content will be emptied, after this the patient passes very little faecal matter, but a whitish gelatinous mucus flecked with blood, and later, bright-red gelatinous mucus, which has exactly the appearance of red-currant jelly, is very viscid and adheres to the bed-pan, in a background of brown watery fluid. The stool has an albuminous smell and an alkaline reaction.

Microscopically it is a very cellular picture, with very few bacilli and little debris to be seen, the cells are (a) polymorphonuclears showing little degenerative change, (b) red cells lying singly or in small rouleaux.

**Blood picture**—There is nearly always a slight but distinct leucocytosis, which does not however usually rise above 15 000 per c mm, there is a relative increase in polymorphonuclears. This leucocytosis is absent in the later stages, and there may even be a slight leucopenia. In the acute choleraic attacks of Shiga account of the fluid loss in the later stages, there is. In chronic dysentery there is very frequently a macrocytic anaemia of nutritional origin.

### SYMPTOMATOLOGY

The clinical attacks caused by the specific dysentery organisms vary from a mild diarrhoea, in which the patient is scarcely inconvenienced at all, to a very severe toxæmic attack which simulates a severe attack of cholera, in neither of these extreme cases does the true dysentery picture appear. The fully developed syndrome also shows a wide range of variations, from the case in which blood and mucus are passed for a few

in contrast to the incubation period in amoebic infection which is often very long

other symptom,  
which is also very

with fever and continuous dysenteric stools which, even if the patient recovers eventually, will lead to a chronic dysenteric condition with permanent inflammation of the large intestine that will

will depend on the virulence of the organism, the resistance of the patient, and the treatment given

In severe Shiga infections, the onset may be with a mild diarrhoea and very little fever, the condition becomes rapidly worse, with the development of fever and the passage of innumerable stools consisting of pure blood and mucus, exhaustion follows rapidly, and early death occurs. On the other hand, the symptoms may be mainly due to the toxic action of this organism—cyanosis and later extreme pallor, a fall of blood pressure, abatement or disappearance of abdominal pain and tenesmus, the passage of profuse watery stools, and vomiting, or sometimes abdominal distension and/or acute dilatation of the stomach, conditions suggesting cholera of

—and at some subsequent date a relapse, which may be much more severe than the original attack, may be precipitated by some secondary factor,

is very acute attack with  
æmia, and death in a few  
days, and for the choleraic type, no further description is needed than the statement that the attack simulates cholera (*qv*). In the typhoid type, after the acute dysenteric symptoms have subsided, the general condition of the patient does not improve, the temperature continues, and a toxæmic state develops.

**Recurring, or relapsing bacillary dysentery**—It is very often the experience of new arrivals in a tropical country that they suffer a succession of mild attacks of dysentery, which keep them in a continual state of sub-health, for a period of a year or more. If none of these attacks has been very  
further  
and possibly suffer no  
in the country

rather than relapsing  
dysentery, as they are almost certainly examples of reinfection with different strains of dysentery bacilli, which continue until the individual has acquired a specific immunity to all the common local strains, or a group immunity that is sufficiently well developed to afford protection against all allied dysenteric strains. If a careful bacteriological examination is carried out, it will usually be possible to isolate a Flexner-group bacillus, or more rarely an organism of one of the other species, on each occasion.

Those who are less fortunate will include in their early experiences one or more attacks of a much more severe kind, which will leave their bowel mucosa considerably damaged so that it is never quite one-hundred-per-cent functionally efficient, and possibly with a number of healed ulcers, the bacterial layer of mucous membrane over  
near the  
circum  
stool,  
the day they may have no further trouble. In these cases, the main dysfunction appears to be failure of absorption in the lower bowel. Periodically, as the result of a chill or a dietetic indiscretion, or some other cause they will have a relatively mild  
with the passage of mucus but pro  
and perhaps mild constitutional symptoms  
these occasions dysentery organism  
this is certainly not the rule, and

patients who are incidentally carriers that the dysentery organisms are recovered from them. This condition is really accidental cause. These cases are usually mild but they are really mild forms of

**Chronic (bacillary) dysentery**—The distinction between this group and the acute form is not clear.

Knees, ankles, wrists, elbows, fingers occasionally the sterno-clavicular and joints. One characteristic is the habit of flitting from joint to joint. This condition varies in different localities, and in some places it is rare, and in others it is common. The pain is out of proportion to the tenderness and swelling which may be very slight. On the other hand hydrarthrosis especially of the knee joints is not uncommon. The fluid is usually sterile but contains the specific dysentery agglutins, often in relatively high titre.

Arthritis usually appears within the first few weeks of the attack, but on some occasions the onset is postponed for as long as three months. The condition is usually mild.

**Ocular lesions**—Conjunctivitis, or anterior uveitis coming on during convalescence. There is marked tenderness photophobia, and blepharospasm.

Acute parotitis is not uncommon and in some epidemics an acute suppurative parotitis has been described.

**Intussusception** is not uncommon in children and a lookout for a recurrence should be kept.

**Complications**—In bacillary dysentery to which is added there being loss of muscular spasms and cramps, and a condition persisting for a month or so.

**Nutritional disorders**—Malnutrition is often seen in the acute stage. It is especially marked in the acute stage. The acute stage is characterized by peritonitis, sepsis, and other disorders of the bowels.

be an indirect sequel due to liver damage. Napier and Neal Edwards (1941) considered that there was an association between macrocytic anæmia in pregnancy and bowel disorders, and the writer (Napier, 1939) has frequently associated nutritional macrocytic anæmia with diarrhoea and dysentery.

**Terminal**—The patient with relapsing dysentery who does not receive appropriate treatment, or who fails to respond to treatment, will usually die of exhaustion and asthenia, but pneumonia as a terminal event is not uncommon in cold climates.

## DIAGNOSIS

any  
treat  
and  
shiga  
betwe  
cated  
always

and the only diagnosis is given at the end of this section.

The milder forms of bacillary dysentery may be difficult to distinguish from ordinary digestive upsets, and the fulminant choleraic type from true cholera. In view of the possibilities of more serious development an accurate diagnosis in the milder types is important to the patient himself, and, from a public health point of view, as a signal to tighten up all sanitary precautions, it is even more important that the true nature of such an infection should be revealed. In the choleraic attack of dysentery, the immediate treatment is practically the same as for true cholera (intravenous saline solution).

public health point of view the far greater

**Stool examination**—A very valuable information. In Mesopotamia during the 1914-18 war, the writer knew a competent pathologist who claimed that he could make as accurate a diagnosis by inspection and a piece of litmus paper as with a microscope, however, he only adopted the procedure during the worst rush periods.

**Bacteriological examination**—The two most important points for the

The sequence is so often as follows—In the case of a subacute attack the physician is not called in for the first few days, he then calls at the patient's house and makes a provisional diagnosis of dysentery, but the patient has not

mucus a loopful of fluid stool should be stroked across the plate or tubes \*

\* There are several new selective media on which the growth of the ordinary saprophytic organisms in the stools is inhibited so that the pathogenic organisms grow and are easily identified. A good example of such a medium is SS (Shigella Salmonella) agar the composition of which is as follows —

Bacto beef extract	50 grammes
Proteose peptone	50
Bacto lactose	100
Bacto bile salts no 3	8.5
Sodium citrate	8.5
thiosulphate	8.5
Ferric citrate	10 grammes
Bacto agar	170 grammes
Bacto neutral red	0.025 grammes

To prepare the medium for use suspend 635 grammes in 1,000 ccm of cold distilled water. Boil for a minute or two to dissolve the medium completely. Do

medium and prepared a medium which also unfortunately has many foreign ingredients. In the writer's personal experience very good results have been obtained with this medium in enteric dysentery and cholera cases.

The constituents are —

Lemco (Oxo Ltd)	0.50 per cent
Peptone (Difco)	0.50
Sodium taurocholate	0.85
citrate (Merck)	0.80
thiosulphate (Merck)	0.85
phosphate (Merck)	0.75
Ferric citrate	0.30
Lactose (Merck)	0.25
Agar	2.50
Neutral red 0.25 per cent (Grubler and Co)	1.5 ccm to 100 ccm

Stock agar prepared from Lemco peptone bile salts and agar 7.0 pH is kept ready in 100 ccm quantities. This is melted and to it sodium citrate sodium thiosulphate ferric citrate and neutral red in the requisite quantities are added.

Sodium hydroxide (2 N) 0.5 ccm is then added to make the final pH 7.4 the medium is then boiled for two minutes and poured into plates.

These media should be inoculated heavily with a generous sample of stool



As has been indicated above, the percentage of positive findings will vary considerably in different circumstances, and will depend on the nature of the stools and the stage of the disease (*see* p 403)

**Serum agglutination** — Though suggestive agglutinations will often be obtained (*vide supra*), this method is of little practical value in the diagnosis of bacillary dysentery, on account of the late development and the relatively low titre of the agglutinins, even as a measure of retrospective diagnosis, its value is limited on account of the early decline of the agglutinins

sigmoidoscopy is not only extremely painful, but may be dangerous in the very acute stages of the disease. In the ordinary acute, in the sub-acute, and in the chronic types, it may be very valuable as a diagnostic procedure, a guide to treatment, and an indicator of progress under treatment. The

by taking swab specimens directly from the ulcerated surface and examining them

In an acute or sub-acute dysentery in which blood and mucus is being passed, if there is no general inflammation of the mucous membrane, bacillary dysentery can usually be excluded, and a diagnosis of amoebic dysentery made

**Technique** — In

able to prescribe a previous night and followed by an enema

washout should not be retained and the patient must be encouraged to pass them by gentle exercise if possible. Nervous or sensitive patients should be given

into the rectum it is essential that the instrument must only be advanced when the operator can see a clear passage which will often have to be created by gentle inflation. By means of sterile swabs specimens can be taken directly from the ulcers for culture and/or microscopical examination

## PREVENTION

The application of the general principles of sanitation, especially with reference to water supply, food, faeces disposal, and flies, is the only real

TABLE VIII  
Contrasting bacillary and amœbic dysentery

	Bacillary dysentery	Amœbic dysentery
EPIDEMIOLOGY	Epidemic in temperate climates endemic and epidemic in tropics Common in children	Endemic and rarely epidemic mainly tropical
PATHOLOGY		
Bowel	Depressed serpiginous ulcers often transverse in thickened and inflamed mucous membrane Sigmoid and rectum mainly also lower end ileum	Less frequent in children Deep oval or round ulcers with raised undermined edges in healthy mucous membrane all layers affected caecum and flexures never ileum
Stools	Very frequent scanty viscid mucous non-offensive bright red blood or red currant jelly Alkaline	Less frequent faecal bulky, offensive dark blood and mucus or anchovy sauce Acid
Blood	Very cellular polymorphs (not degenerated) columnar epithelial cells and macrophages RBCs discrete	Not very cellular degenerated lymphocytes clumped RBCs Charcot Leyden crystals active amœbæ containing red cells
SYMPTOMATOLOGY		
Incubation	Leucocytosis only in acute stages subsequently normal or leucopenia	Usually leucocytosis increases with liver abscesses
Onset	A week or less	A fortnight to many months
Fever	Acute	More often mild ones
Abdominal pain and tenderness	Usual	Rare
Tenesmus	Severe localizing to left side	Variable may be severe localizing to right side
Terminal	Usually severe	Less severe often absent
Complications and sequelæ	Typhoid and exhaustion Few polyarthritides	Exhaustion and complications Peritonitis and hæmorrhage hepatitis and liver abscesses common Multifarious sequelæ
SIGMOIDOSCOPY	Not good practice in acute stages red inflamed mucous membrane readily bleeds rigid bowel wall ulcers seldom seen	Pernicious in sub-acute attack raised button like ulcers or numerous minute ulcers (mouse-eaten appearance) with red edges in normal mucous membrane
THERAPEUTIC TEST	No response to emetine	Marked improvement with three 1-grain doses emetine on three successive days

A marked fall in the incidence of dysentery in a community such as a tea garden labour force follows the introduction of protected water supply a further reduction almost to the point of elimination will be achieved by the establishment of a satisfactory latrine system when this is possible. In institutions and other communities which have common feeding arrangements a careful search for carriers should be made amongst food handlers, and dysentery convalescents should not be employed in this capacity at least for many months and after repeated bacteriological examinations. There is no evidence that prophylactic inoculation is of any value.

#### RURAL SANITATION

Rural water supplies and water disinfection have been discussed above (p. 396). Reference to rural sanitation would perhaps be appropriate here. Rural sanitation, particularly in India, is not a problem that is likely to be solved by any single formula; the conditions are far too varied. However, the

one recent advance in sanitary engineering that has come nearest to providing this solution is the bored hole latrine. Notes on this subject, kindly given to me by Mr B R Dyer, professor of sanitary engineering at the All India Institute of Hygiene, Calcutta, have been published in the Indian Medical Gazette by Mr G Ghosh (1942) of

the flow

The advantage of the bored hole latrine is that it is easy to install and very cheap, having a small diameter, the faeces are incorporated quickly in the soil in the bored hole. There is no smell when the surface of the content of the latrine is more than 3 feet from the ground surface and there is no breeding of flies. It is more hygienic than the open latrine, that in 6 months after a bored hole latrine has been the soil. The life of a bored hole latrine is 10 years after the hole has been filled to and abandoned, the squatting plate and

the superstructure can be moved to another site.

Construction.—The bored-hole latrine is a round hole bored into the earth with special auger 18 inches in diameter. The depth to which it is bored depends on the sub-soil water level. There should be a minimum of about 3 feet of water during the dry season.

A hole about 6 inches deep and 18 inches in diameter is first dug and the When the auger is put back into the hole it should be protected by

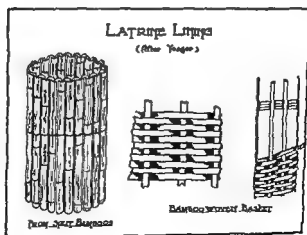


Figure 125

**Squatting plate.**—This should be of reinforced concrete. Squatting plates 3 feet by 2 feet 6 inches are made of cement concrete in the following proportions: cement 1 part, sand 3 parts, stone or brick chips ( $\frac{1}{2}$  inch to  $\frac{3}{4}$  inch) 4 parts.

The thickness of the plate throughout is 2 inches. The plate is sloped  $1\frac{1}{2}$  inches from edges to centre. The concrete is reinforced with  $\frac{1}{4}$  inch diameter rods (figure 126)

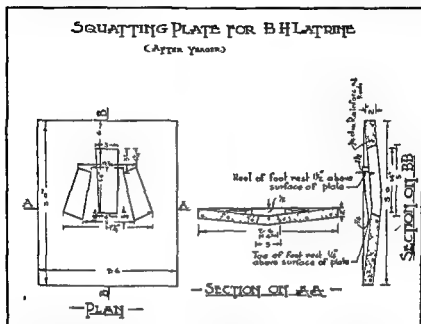


Figure 126

The bare squatting plate with the hole is first cast in a mould. After 24 hours it is removed from the mould and the top surface is smoothed and the foot rests are added.

It should be noted that the face of the hole in the squatting plate is splayed out at the top and bottom.

under water for a latrine.

An inexpensive bamboo poles.

## TREATMENT

**Introduction**—Sojourners in the tropics as well as the indigenous inhabitants are apt to take a light view of an attack of diarrhoea or mild dysentery, but, since at least 75 per cent of chronic ill health in the sojourner can be attributed to malaria or dysentery—and in some places malaria is unimportant—there is every reason why their medical advisers should take great care not to fall into the same error. In the present state of

medicine against most subsequent infections, if they are not so treated, they will eventually pass through the relapsing and chronic stages to become a permanent semi-invalid with periodically recurring ulcerative colitis. Further, the risk of serious development of the initially mild attack must be fully appreciated.

The specific treatment of bacillary dysentery has always been singularly unsatisfactory. Antitoxic serum, which was introduced about

40 years ago, is of undoubted value, and its dramatic effects in certain cases leave a great impression on the minds of those who see these, but it has never really touched the main problem of the treatment of the millions who suffer from this disease. The main reasons for this are that the serum is

cases of other dysentery infections, and, finally, the vast majority of cases have to be treated under conditions where serum treatment would be difficult or impossible, and or elaborate, and not ent

With the introduction again raised that some of these might be of value in bacillary dysentery.

Little success was achieved in this direction until recently, though a few observers are of the opinion that some of the antiseptical drugs such as yatren and carbarone (*vide infra*), have a specific action in bacillary infection, this view is not generally accepted. The early sulphonamides gave disappointing results, though in some chronic cases they appeared to help towards the eradication of mixed secondary infections.

Rather surprisingly, sulphapyridine was not used in the treatment of

does, and its success probably depends on its reaching the large intestine in sufficient concentration.

The most common method of administration is by mouth. It is given in much larger doses than in other diseases. The results seem to suggest that treatment of time other than this is not satisfactory.

**Procedure —**  
toxaemia ulcerative  
ways be kept in r

Whenever possible, the patient should be kept in bed, but the main thing but the main thing to defæcate but a precaution may well make the difference between death and recovery, though of course very frequently circumstances are such that it cannot be observed. At first, practically no food should be given, but a free supply of glucose water or plain water, and later albumin water, lime whey, and chicken broth may be allowed.

In the mild non-toxaemic case 60 grains of sodium sulphate should be given in half a glass of water every two hours during the first 24 hours.

placed by the patient's bed and he should be encouraged to get up as frequently as possible.

In the more severe cases, sulphamyl guanidine should be given. This must be given in full doses, 0.10 gramme per kilogramme body-weight of

patient for the initial dose and 0.05 gramme for subsequent doses every

lower two grammes as an initial dose and one gramme three hourly in an adult will usually be sufficient

remembered that opium is definitely contra indicated in cholera

**Anti dysenteric serum** — Shiga antitoxic serum as opposed to the so called polyvalent serum should be used for a number of reasons the Flexner organism gives rise to a serum of very low antitoxic quality. Flexner infections seldom need antitoxic serum treatment and when serum is given they seem to respond as well to anti Shiga as to the polyvalent serum

The antitoxic serum that is usually available to day is concentrated and contains about 5000 antitoxic units to the cubic centimetre. An initial dose of 100,000 units may be looked upon as maximum and very often 50,000 units will be sufficient a dose of 50,000 units should be given

red dose if it appears to be indicated serum should be given intravenously in normal saline. In a cold room the serum should be warmed to body temperature before use. It may follow the administration of morphine but should be tested very carefully. Intramuscular or subcutaneous injections are less satisfactory as the serum is absorbed slowly and may cause a local reaction. The modern serum is treated with a proteolytic enzyme so that the danger of anaphylaxis is considerably reduced if not eliminated but in patients who have previously received any form of serum treatment and if time permits it may be advisable to precede the intravenous injections by the desensitizing course mentioned below

There is usually some reaction to the serum treatment after about 12 hours in the form of flushing of the face a slight rise of temperature and temporary exacerbation of symptoms but these rapidly pass off and general improvement is soon noted

collapse and they should be countered by injections of adrenaline and pituitin, or (b) the later serum sickness that may come on six to ten days after the serum is administered with local pain at the site of the injection fever joint pains and urticaria. A daily dose of calcium lactate will reduce the chances of both these reactions occurring.

**Intravenous therapy**—In severe cases, whether of the choleraic type or not, this will often be indicated, and it is useful as a vehicle for the antitoxic serum. Glucose added to physiological saline (25 grammes to 500 ccm., or about a pint) is the best for the ordinary severe case, but for the choleraic type of attack, hypertonic saline will probably be more

**Bacteriophage**—There is unanimity of scientific opinion on the fact that, *in vivo*, bacteriophage does not act as it does *in vitro*, and lyse the dysentery bacilli in the tissues. The explanations of its action—if it has any action—that seems most feasible are that it converts pathogenic bacilli into non pathogenic or less pathogenic organisms, or that the lysate of those organisms that it does lyse, acts as a vaccine. The writer has never been convinced from his own experience that bacteriophage has any specific action, but it is impossible to ignore the opinion of many experienced practitioners who claim that it is of definite value. Some of these say that it cuts short the attack when given in doses of one ampoule (about 2 c cm) every 4 hours, others claim that it is useless in these small doses, and that to obtain any results at all it must be given in large doses, 4 to 6 ampoules every two hours.

To summarize, world scientific opinion is still very sceptical regarding case, the writer however doses, even the sceptic is innherally applicable to ies in this case

ounces of

R Extracti opii sicc	gr ii
belladonnæ sicc	gr $\frac{1}{2}$
Cocobutter	ad 12

	gr	n
	gr	1
ad	12	

**Vesical tenesmus and strangury** will be assisted by a belladonna and alkali mixture —

R Potassa bicarbonatis  
Tinctura belladonnae  
                  hyocyami  
Infusum buchu

• gr xx  
m xx  
3js  
ad 3js  
4 times daily

This will also  
indicated above  
vented by careful

1 warm rectal washes  
it stools can be pre  
plication of lanoline,

or calamine lotion made with an oily base. Meteorism may be an indication of severe toxæmia but in the later stages of the disease it often indicates an indiscretion in diet. It may be relieved by giving charcoal biscuits or charkaolin but more active treatment with turpentine stupes, etc (see p 475) may be necessary. Vomiting and hiccough may also be

also to give some form of fruit and in India and other countries where sherbet for drinking or other fruits as long as the feeds should be every two hours. The diet

must be extended slowly there is a strong tradition against the use of milk in dysentery to be excluded although be citrated given or better still fort good alternative at a later stage very use ful in more chronic forms of intestinal flora. Then eggs in the for ellies and veg +

pre Special diets—Great success has been claimed for the apple diet. As

available

the first day followed by bismuth carbonate in doses of gr. ss three times a day until the symptoms subside. Then to prevent further recurrence the diet will have to be regulated very carefully for some time (see below) and ispaghula (or one of the proprietary preparations Isogel Normacol etc) a tablespoonful nightly and liquid extract of kurchi, a drachm three times a day taken for a number of weeks. The best form of



for a time, but the possibility that these absorb and retain vitamins must be remembered. When some other purgative is necessary, senna pods should be used.

enemata that are the mainstay of the treatment for this latter condition.

**Vaccines.**—These have never found any place in the treatment of the acute attack. Their advocates have claimed useful results in chronic cases in which the original causal organisms are still present. For these they advocate autogenous, or at least homologous, dysentery-group vaccines, as well as 'sensitized' vaccines, prepared by treating the vaccines with homologous serum.

Others have used autogenous vaccines of various other organisms obtained from the patient's stool, on the assumption that they are the organisms causing the secondary infection of the ulcers, sometimes picking out certain special organisms, e.g. *Bact. pseudo-carolinus*, which—for no very apparent reason—they particularly suspect. The writer has seen striking results follow the administration of these vaccines in certain cases, which results he attributes to a combination of psychological effect and protein shock.

If such vaccines are used with a full appreciation of their limitations—which of course must on no account be conveyed to the patient—they are sometimes of value in certain cases of chronic bacillary and amoebic dysentery.

Vaccines prepared from cultures taken directly from the ulcer by means of the sigmoidoscope are on a slightly higher scientific plane, but have not been any more successful in the writer's experience.

**Diet in recurring dysentery,** when acute symptoms have subsided or

Bengal food or Horlick's milk at 7 a.m., or on waking and again last thing at night.

For breakfast sieved porridge with milk, lightly boiled or poached eggs dry toast and butter with honey or marmite. Weak tea with plenty of milk.

At lunch and dinner cream soups, steamed fish or chicken, preferably minced or creamed, but may be taken in the ordinary way if well masticated, mutton may

Orange juice, and adexolin or some other vitamin concentrates (A and B) should be taken in adequate doses 2 or 3 times a day.

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## FLIES

THE following note on flies and methods of controlling them has been prepared from notes kindly given to me by Dr. D. N. Roy, the Professor of Entomology at the School of Tropical Medicine, Calcutta

*Method of spreading infection* The three ways by which flies spread infection are, (i) by passing ingested pathogenic micro-organisms with their excreta, (ii) by

bottle found in the house is *Chrysomya megacephala* and among the flesh flies

## CONTROL OF FLIES

The menace of flies may be reduced in three ways, by eliminating or reducing their breeding outside the house, by killing the adults inside the house, and by screening the house, or at least the kitchen, pantry, and dining room

It is seldom possible completely to eradicate flies, but their number can usually be reduced by proper measures

houses

logical

The chemicals for treating manure are potassium permanganate, hellebore, borax and fluo-silicate

One drachm of potassium permanganate in 8 gallons of water is sufficient for 10 cubic feet of manure

Half a pound of powdered hellebore should be mixed with 10 gallons of water, and the mixture allowed to stand for 24 hours, one gallon per cubic foot of the fluid is sprayed on the manure

One pound of powdered borax for every 16 cubic feet of manure should be mixed with the manure heap by stirring. Borax, when used in such small quantities, has no harmful effect on crops when the manure is later used for fertilizing purposes

One pound of sodium fluo-silicate in 15 gallons of water is applied to manure until it is fully soaked

Under this heading, pyrethrum powder might be included, but its use is not economical

times a week. Shallow trench latrines used mainly at *melas* should be filled up with dry grass and leaves and burnt out or they should be covered with earth, new trenches being used each day. Human faeces should never be buried in trenches less than 4 feet deep.

The type of latrine which completely eliminates fly breeding is the bore-hole latrine (*vide supra*).

Incinerating night-soil and street refuse has not proved as successful as was once thought. The disadvantages are many: it is doubtful if it can be conducted in such a way as to eliminate the breeding of *Musca* in and around the incinerator. Further, it is very wasteful.

**Screening.** For economic reasons the screening of the entire house is seldom possible. All foodstuffs including milk should however be kept screened. The dining room should be screened. Ways of destroying flies are by poison-surface but swatting will in some arsenic used in the form of sodium serious accidents are likely to occur. Iodohyde is one of the most commonly

container

The destruction of adult flies can be accomplished very effectively by the use of pyrethrum sprays as used for mosquitoes. On walls DDT paints and sprays retain for many weeks their powers of destroying flies that settle on the treated areas.

# AMÆBIC DYSENTERY

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**Definition**—A dysenteric affection that is a condition characterized by ulceration of the large intestine and the passage of numerous stools containing blood and mucus which may be acute or chronic and is caused by the protozoal parasite *Entamoeba histolytica*

**Discussion**—There is a very strong tendency in the literature of the

a very large number of amœbæ and several of these infect man the term might imply infection by any one of a number of species of amœbæ whereas it only refers to infection by one and (iii) that whilst suggesting that the parasite attacks a number of different tissues and causes a variety of pathological changes in these which is a fact it also implies that the processes are independent whereas they are all secondary and dependent on the primary intestinal ulceration

For these reasons the writer prefers to consider the subject under the heading amœbic dysentery and to classify the secondary amœbiases' including amœbiasis sine dysentery as complications or sequelæ of the primary infection of the bowel wall which may have been sub clinical There are many parallel examples which the writer could quote in favour as many that could be quoted view as he considers that the rescue tropical medicine from

**Historical**—Amœbic and bacillary dysentery were naturally not differentiated until their respective causative organisms had been identified there were however strong reasons for believing that the two diseases were distinct

tropics, which had been long associated in the astute minds of the early clinicians with hepatitis and liver abscess, was a different disease from the jail or asylum dysentery of temperate climates, which was never followed by these sequelae. As

species where parasitologists have been years

The present war has again revived interest in this subject. Hundreds of thousands of British and American soldiers are serving in the tropics, so that *Entamoeba histolytica* is assured of vast virgin pastures and it is to be hoped that its behaviour will be carefully studied.

#### EPIDEMIOLOGY

**Geographical description**—The disease has a wide distribution in all tropical and sub-tropical countries, in the temperate zone, its position is anomalous, for the percentage of 'carriers' (*vide infra*) is almost as high as in the tropics, but amoebic dysentery is a rare incident, and when genuine autochthonous cases occur in Great Britain, Canada or even the north USA, the incident is usually considered a suitable subject for a special report, which is quoted and requoted in the literature for some years. There are exceptions to this relative rarity, as in the case of the epidemic in the north of England in 1934, in the first, 1,400 cases were traced to visitors returning from this city, 75 per cent of whom had stayed in two villages in the north of England and in the second during the great stockyard fire, which

hence,  
common  
digest-  
fection  
ciliary

in origin

**Seasonal incidence**—As a general rule, there is no special seasonal distribution in the tropics, sporadic cases occurring all the year round. In special circumstances, for example, where flies are the main disseminators, or when contamination of water supplies is more likely to occur at some special season, there may be a tendency for a concentration of cases. In temperate climates it is usually a summer disease.

heavily concentrated in this age period. The sexes appear to be equally  
 a little  
 ut the  
 a com-  
 writer  
 uths in  
 years  
 ane

# ÆTIOLOGY

The causal organism—*Entamæba histolytica*, a protozoan of the family Amœbidae, is the causal organism. It is a two-phase organism with an active trophozoite phase and a resistant cystic phase (see plate A, figures 1 to 3). There are other amœbæ which infect man, all of them are probably non-pathogenic, namely *Entamæba coli*, *Entamæba gingivalis*, *Endolimax nana*, *Dientamæba fragilis*, and *Iodamæba butschlii*.

Morphology.—The trophozoite of *E. histolytica* is an amœboid organism from 15 to 60 microns in the long axis, consisting of a clear

When the organism has been outside the body of its host for some time, however, it changes to a different kind, it then becomes a cyst. The cyst is composed of clear, rounded, refractile cells. The endoplasm contains a spherical nucleus which is vesicular, containing a fine central karyosome, in unstained preparations, it is invisible, in contra-distinction to the clearly visible brighter refractile nucleus of *E. coli*.

The precyst form first becomes immobile, extrudes all food particles,

cytoplasm

is as f  
 action  
 where  
 amœba excysts, the nuclei divide and then the amœba itself divides into eight amœbulae. These remain in the fluid contents of the small intestine and pass through the ileo-cæcal valve; then, escaping from the more solid



and more static contents of the large intestine, they find their way into

by simple binary division, amœbæ find their way into the lumen of the gut, where under the sub-optimal conditions they extrude any contained food, become spherical and form a cyst wall, the nucleus divides by binary fission to produce the characteristic four-nucleated cyst, which eventually passes out with the faeces. Once outside the body no further development takes place.

Alternatively, the active amœbæ, during their invasion of the tissues, may find their way into a vein, when this occurs they are carried via the portal vein into the liver, where they cause first hepatitis, then multiple small abscesses, and eventually a large liver abscess, according to the number of the invading amœbæ and the resistance (possibly aided by therapy) of the host tissues. At whatever stage this process is halted, the result, as far as the amœba is concerned, is the same, it has reached a dead end. Thus, this invasion of the blood stream must be looked upon as the ultimate design of the protozoan species, not the destruction of the host. Secondary invasion is reported a number of times, the contamination of a skin abrasion

around the anus or a colostomy opening.

A single individual will pass many millions of cysts in one day, the number has been estimated as from 300,000 to 45,000,000.

**Culture**—Boeck and Drbohlav (1925) were the first workers to find a satisfactory medium for the culture of amœbæ. The medium generally used is a mixture of serum and egg albumin. The amœbæ tend to crawl up the slant.

**Resistance**—The cysts will survive in sewage for months and for equally long in distilled water, that they will also live in chlorinated water is a fact of some considerable practical and epidemiological importance.

Amœbiac dysentery is a disease of the large intestine, but in some cases, they may invade the liver, lungs, and other organs. The disease is generally self-limiting, but in some cases it may be fatal. The life cycle of the amœba is as follows: The adult amœba lives in the large intestine, where it feeds on bacteria and other food. It may be passed in the stool, where it may develop into a cyst. The cyst may survive in the environment for a long time. When ingested by a new host, the cyst develops into an adult amœba, which then begins its life cycle again.

obtain nourishment and whence they had no symptoms of dysentery. It has been found that all persons who have been in contact with such small animals are liable to develop the disease. The conclusion regarding the transmission of the disease is that it is carried by the faeces of carrier animals.

Amœbiac dysentery is a disease of the large intestine, but in some cases, they may invade the liver, lungs, and other organs. The disease is generally self-limiting, but in some cases it may be fatal. The life cycle of the amœba is as follows: The adult amœba lives in the large intestine, where it feeds on bacteria and other food. It may be passed in the stool, where it may develop into a cyst. The cyst may survive in the environment for a long time. When ingested by a new host, the cyst develops into an adult amœba, which then begins its life cycle again.

stools—in different populations have been carried out for many years

placed at above 20 per cent by various competent observers Knowles and Das Gupta found *histolytica* cysts in 10.87 per cent of stools from an unselected population in Calcutta, this finding at a single examination suggests that at least double this number were actual carriers

Data are available for many countries, but no more need be quoted here, all these observations indicate that in most countries in the world there is a high percentage of carriers, and that though on the whole the percentage is highest in the tropics and in sanitarially backward countries and communities the differences are not very great, nevertheless, except for rare incidents in temperate countries amœbic dysentery is confined to the countries usually giving bowel disorder, and, so 'amœbiasis' (vide slender

there is usually a higher percentage of carriers amongst convalescents, and 'contacts', e.g. soldiers returning from tropical countries where the disease has been rife

**Source route and dissemination of infection**—The resistant cyst is the only infective form, as the delicate trophozoite would obviously not resist the digestive juices, even if it survived long enough to be ingested. A few animals have been found infected in nature—monkeys rats and dogs—and though it is possible to infect both cats or dogs in the laboratory (vide supra) they do not normally pass cysts and are therefore not sources of infection. Man is thus probably the only important source of infection. In patients suffering from acute amœbic dysentery, the active trophozoite forms which find their way into the intestinal lumen are swept out with the rest of the intestinal contents rapidly die and are incapable of becoming a source

nor the convalescent carrier but the carrier who has never suffered from a clinical attack of dysentery. However, in the opinion of the writer the epidemiological and other evidence makes it very questionable whether these symptom free carriers especially those that are encountered in temperate climates can be in any way associated with the dissemination of the disease, amœbic dysentery though the 'convalescent carrier' and the 'contact carrier' should be regarded with considerable suspicion, and should not be employed as food handlers

Invasion is always by the oral route

The media in which the infection spreads are food and water. The former may become infected by means of flies—but these are not usually considered as important as they are in bacillary dysentery—by food-handlers, or by the contamination of greenstuffs with human sewage used as manure. Water may be directly contaminated by human sewage, as in the historical Chicago incidents (vide supra) and it must be remembered that chemical disinfection, e.g. chlorination, does not kill the cysts

**Immunity and susceptibility**—Though there is probably no such thing as complete natural immunity, there is evidence of varying susceptibility in different individuals, in a population exposed to infection, some escape

infection altogether, others harbour the amoebae and pass cysts for a time without showing any symptoms, yet others suffer from mild dysenteric or diarrhoeal symptoms, while, finally, others will suffer from a serious or fulminating dysentery

There is not much evidence of individual acquired immunity, one on the  
 ily less  
 ists  
 rs but  
 British  
 soldiers

There is some evidence of immunological response—as distinct from immunity—as complement fixation occurs when antigen prepared from cultures of *Entamoeba histolytica* is brought in contact with the serum of an infected person (*vide infra*)

### PATHOLOGY

**The colonic lesions.** Site.—The initial ulcers are in a very large percentage of cases in the caecum, after this the common sites are the ascending colon, the sigmoid, and the rectum. The secondary ulcers are more widespread, and occur with almost equal frequency in all parts of the large intestine. This is well shown in the diagram below

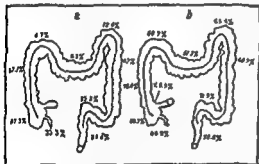


Figure 127 Showing common sites of amoebic ulcers (a) Distribution of lesions in 63 cases with only one or two ulcers (probably primary) (b) Distribution of lesions in 188 cases of all types (after Clark 1925)

The ileo-caecal valve is sometimes involved, but never the ileum proper

**Mechanism of production.**—The amoebae find their way into Lieberkuhn's crypts, from there they penetrate the mucous membrane, but they do not cause much inflammatory reaction until they reach the sub-mucosa, here they secrete a cytolytic which acts on the local tissues causing an outpouring of fluid into these tissues stasis and eventually thrombosis in the capillaries in these areas, and coagulation necrosis. The

necrotic  
 infiltrate  
 forms  
 into

ment of the larger vessels, with resultant severe hæmorrhages, and possibly interference with the circulation, and gangrene of a portion of the gut, if these conditions inevitably lead to perforation and peritonitis.

ous and separate, and in extreme cases through the whole thickness of the gut wall. (d) Finally, in the healing process, the ulcer contracts and covers the base, or (e)

to the patient, danger to the tissues

Another type of lesion that is usually associated with milder clinical carrier state is one in which there are ulcers, which give the mucous membrane these ulcers for some reason (not further specified). Simple abrasions of the mucous membrane which are believed to heal up rapidly have also been observed, but the complete

undermined, with a base of granulation tissue on the muscular coat, there is a general thickening of the bowel, in which all layers take part. Amœbæ are still present in the deep tissues and although most of the inflammatory processes are caused by secondarily infecting organisms, healing will not take place while the amœbæ are still there. When the amœbæ are eradicated, the ulcer either (a) heals leaving a scarred mucous surface, or (b) contracts and forms a stricture of the bowel, which is usually quite free from much the same

conditions as does the vacuaty ulcer.

**Secondary extra-colonic lesions**—The commonest site is the liver,

usually in the left lobe infection. The lesions are much larger than those in the gut, to 1, the latter size and direction of the two

is due to some extent on the number of organisms, probably to a greater extent on the virulence of the parasite, and to this parasitic invasion—

livers already overworked or otherwise damaged being much less likely to resist such invasion—and, later, on the presence or absence of secondary infection. The pathological process may go through the following four stages to reach the final one, or it may be halted at any one of them—

(a) *hepatitis*, (b) *miliary abscesses*, (c) *large 'sterile' abscess or abscesses*, (d) *secondarily infected abscess or abscesses*, or (e) *an abscess may point and burst through the skin, or into some other organ or tissue* (*vide infra*)

it fails, and

which develop

stage, in which

abscesses—if not, these abscesses grow and eventually coalesce producing

a single large abscess

of a necrotic mass of

no true pus. The cav-

are still active, and

which the amœbæ have not succeeded in 'lysing'. The abscess may extend

and eventually burst into some other organ or tissue, but there is evidence

that the process is self-limiting here so far from any evidence of secondary

evidence of secondary

the abscess may be a

necrotic material becoming

eventually calcified

On the other hand, it is not uncommon for the abscess to become

secondarily infected via the blood or the bile ducts, or by direct extension

in which it becomes

and will

perish

active abscess these can be found by scraping the cyst wall. A secondarily infected abscess will consist largely of pus and liver-cell debris.

Abscesses in other organs—Pulmonary abscess secondary to liver abscess is comparatively common, but so called primary lung abscesses have been described. 'Primary' in this instance is meant to indicate 'without the intermediary liver abscess', it is not a truly primary condition.

Brain and spleen abscesses are not very uncommon and are always secondary to liver abscess.

Ulceration of the skin—It is doubtful if the amœbæ could ever penetrate the epidermis, but, once through into the deeper layers of the true skin, they are able to penetrate rapidly, to cause gangrene of large areas

of focal coagulation necrosis

tion may take place at this

to absorption of these minute

eventually coalesce producing



Figure 128  
Charcot-Leyden  
crystals

of skin and to produce deep punched out ulcers. The sites are practically always around the anus or a colostomy wound.

**The blood**—There is always a sharp leucocytosis during the acute attack the count often rising to 30 000 per c mm. The increase is general and the white blood count is usually normal.

usually normal  
complicated by  
will usually be

macrocytic

**The faeces**. The characteristic amœbic dysentery stool is bulky and offensive containing anchovy sauce pus much mucus and dark red blood often in clots mixed with faecal matter at first later the stool may consist of little more than anchovy sauce pus and dark blood and in severe cases gangrenous clots which give it a very offensive smell.

The reaction is acid.

**Microscopically** the stool does not present a highly cellular picture there are many bacteria yeasts and other organisms and undigested food debris the cells that are present are mainly lymphocytes with some polymorphonuclears (both degenerated and possibly only represented by a pyknotic mass of nuclear chromatin so that their identity may be uncertain) clumped red cells Charcot Leyden crystals and active amœbæ (For further details and methods of examination see Diagnosis)

## SYMPTOMATOLOGY

**Incubation period**—This is usually from 7 to 14 days but it may be many months and if the onset is insidious the first serious symptoms attributable to the amœbæ may be delayed for many years when perhaps the patient has

**Clinical**  
occur when the  
venience of diagnosis

is no essential difference except in degree in the pathology of these various types —

- (a) *The fulminant attack*
- (b) *The typical acute attack*
- (c) *The diarrhoeal onset*
- (d) *Chronic amœbic dysentery*
- (e) *The latent infection*

gangrene of a loop of intestine fortunately a comparatively rare incident there may be before the final collapse a short period when local signs and

symptoms subside and stools decrease, but this is accompanied by a rapidly increasing toxæmia which any physician should recognize

(b) In the typical acute attack, the onset may be sudden with the passage of 10 to 20 stools a day, containing blood, mucus, and pus. At first diffuse, then later may be tenesmus as in the typical attack.

(c) Perhaps the most common type of onset is the diarrhoeal onset in which all the signs and symptoms noted above in the typical attack may be present.

(d) Chronic amoebic dysentery — For this condition the term chronic amoebiasis seems justifiable. It is, as a rule, secondary to one of the acute or sub-acute types described above, but it is not uncommon to find the condition established in a patient who gives no previous history of dysentery or diarrhoea, however in such cases the infection has obviously been present, though latent, in the patient for some time. The main symptoms are repeated attacks of loose stools, possibly with a little blood and mucus, alternating with periods of constipation, accompanied by slight pain and distinct tenderness in the abdomen most commonly in the area of the cæcum, descending colon, and sigmoid, the liver is tender, and a thickened bowel will often be felt distinctly through the abdominal wall. There is a muddy or yellowish discoloration of the skin, and a history of loss of weight, indigestion, loss of appetite, and slight general malaise. A large number of secondary symptoms can be noted.

the chronic stage, the liver complications often being the first indication of the more serious nature of the condition, or a typical attack with the passage of blood or pus, or even a fulminant attack may develop from this mild beginning.

(d) Chronic amoebic dysentery — For this condition the term chronic amoebiasis seems justifiable. It is, as a rule, secondary to one of the acute or sub-acute types described above, but it is not uncommon to find the condition established in a patient who gives no previous history of dysentery or diarrhoea, however in such cases the infection has obviously been present, though latent, in the patient for some time. The main symptoms are repeated attacks of loose stools, possibly with a little blood and mucus, alternating with periods of constipation, accompanied by slight pain and distinct tenderness in the abdomen most commonly in the area of the cæcum, descending colon, and sigmoid, the liver is tender, and a thickened bowel will often be felt distinctly through the abdominal wall. There is a muddy or yellowish discoloration of the skin, and a history of loss of weight, indigestion, loss of appetite, and slight general malaise. A large number of secondary symptoms can be noted.

is are absorbed

often occurs without any of the above clinical forms resumed in retrospect from

last paragraph, from which the patient may be suffering, are due to this condition. But the writer questions the justification of arriving at this conclusion solely on the evidence of the stool and the presence of cysts which

have the morphological appearance of *histolytica* cysts or of applying the term amœbiasis *sine* dysentery to these laboratory diagnosed cases

### COMPLICATIONS

The commonest complications are *hepatitis* and *liver abscess* these will be considered separately as though they are ætiologically linked with amœbic dysentery they constitute a separate syndrome Other complications are —

**Hæmorrhages**—The deep sloughing that occurs in the bowel wall often

of the bowel wall at the site of a deep ulcer this is an uncommon accident and seldom occurs except in the case of gangrene of a segment of the colon which subsequently ruptures

operation Retro colonic abscesses also may occur as the results of a leak from or the frank perforation of an amœbic ulcer retro peritoneally The signs and symptoms will be very similar to those of an appendix abscess and will often be in the locality of the cæcum to make the picture more

omy  
g of  
the  
the

muscle layer very painful on pressure and exuding a purulent discharge The ulceration is liable to spread with alarming rapidity unless controlled by emetine injections

Rogers and ... the ... led  
upon as sec  
quency with  
in cases in  
more recent  
dietetic in origin a sequel to restriction or to mal absorption of essential food elements particularly protein

### DIAGNOSIS

The clinical dysenteric attack will have to be differentiated from dysentery from other causes (see p 368)

It is of primary importance that this differentiation should be made in order to ensure the correct treatment (there being radical differences in the treatment for bacillary amœbic and other dysenteric conditions) but it is also important from the point of view of prognosis especially to provide an indication of the complications that are to be expected

Points of differentiation between bacillary and amœbic dysentery are given in table VIII (p 413)



**Laboratory diagnosis—Stool examination**—The first point to be borne in mind is that the examination must be made on a fresh stool. Amœbic trophozoites will not be found unless the specimen is absolutely fresh, even cysts begin to degenerate in an hour or so in some stools. In a cold country, it will be necessary to keep the specimen warm, both before and while it is examined, if the activity of the amœbæ is to be maintained, and it is important for proper identification that they should be active. If possible *e.g.* in chronic cases, the patient should always go to the pathologist and pass a fresh stool for him to examine, rather than send the specimen to the pathologist. If a stool cannot be passed to order, it is a good practice to insert a rubber catheter into the rectum, rotate it so that the end moves about, and from the 'eye' of the catheter it will usually be possible to obtain a small sample suitable for examination.

The stool must be inspected carefully and its macroscopical characteristics noted (*see p. 433*).

The reaction of the stool should be tested with litmus paper, it will be acid in amœbic dysentery.

For microscopical examination, two preparations must be made—(a) in saline and (b) in iodine.

(a) *In saline*. A small portion of stool if possible a piece containing blood or mucus is picked out on a platinum loop and transferred to a watch glass containing a few drops of normal (0.85 per cent) saline, a fine emulsion is made any mucus present being teased (the emulsion should be such that small print can be read through it), a ring of vaseline is arranged on a clean slide, a drop of emulsion is placed in the centre, and a thin coverslip is placed over it. The slide is placed on the microscope stage—which should be warmed if necessary—and examined with a 1/8th objective.

(b) *In iodine-eosin*. A 5-per-cent potassium iodide solution is saturated with iodine, an equal amount of saturated solution of eosin in normal saline is added immediately before use. A portion of stool is added and a slide prepared in saline. There is some advantage in examining the saline and iodine-eosin specimens under the same coverslip.

There is a definite advantage in employing the technique (*see p. 620*) in examining stools for a loopful of material is taken from the

The saline preparation must be examined immediately, and if there is any delay it must be kept in the 37°C incubator, the iodine-eosin specimen may be kept for some hours.

If the examination is to be thorough, several 'smears' of each kind must be made with samples taken from different parts of the stool.

The general microscopical nature of the stool should be noted, and amœbæ should be looked for and, if found, identified. There should be little doubt about the identity of an active trophozoite of *E. histolytica*.

It could only be confused with *Entamoeba nœbæ*, but a sluggish or dead amœba which may show some amœboid movement. Most acute stages are more readily found

than the trophozoites, also have to be differentiated from other amœbic and flagellate cysts, and from *Blastocystis hominis*. About the identity of a single four-nucleated cyst in the saline or in the iodine preparation there will often be doubt, but, when several specimens are found in each, the doubt will usually be removed, of course, frequently both *E. histolytica* and *E. coli* are present.

When trophozoites are present, there are usually few cysts and *vice versa*.

The finding of active *E. histolytica* with contained red cells, or of undoubted precysts, is diagnostic of amœbic dysentery. The presence of

cysts is also said to be diagnostic of some ulceration, but this may be of the pin-point or somewhat questionable shallow type

Culture of the faeces for entamoebæ is a laboratory refinement that is certainly worth undertaking if a well-equipped laboratory is available

In a convalescent at least six consecutive daily examinations should be carried out—and found 'negative'—before a patient can be proclaimed as free from infection

TABLE IX  
Important morphological characters of *E. histolytica* and *E. coli*

	<i>Trophozoite stage unstained E. histolytica</i>	<i>E. coli</i>
Size when rounded	10-30 $\mu$	20-30 $\mu$
Movements	Very active in fresh Later finger like clear podia thrust out from mobile body	-
Colour and appearance	Glassy clear greenish or yellowish	pseudopodia Ground-glass
Inclusions	Red cells usually no bacteria	No red cells* bacteria yeasts, starch granules and even other protozoal organisms
Nucleus	Usually not seen	Usually visible
<i>Encysted stage unstained</i>		
Size	6-20 $\mu$ .	10-33 $\mu$
Shape	Spherical	Spherical
Cyst wall	Thin	Thicker
Colour and appearance	Clear greenish or yellowish	Like ground-glass
Chromatoid bodies	Usually bars with smooth rounded ends present in most cysts	Filamentous or splinter like, seen only in about 5 per cent of the cysts
Glycogen mass	Often very prominent especially at binucleolar stage	Sometimes well marked in early stage but soon disappears
Nuclei	Usually invisible	Visible
<i>Encysted stage iodine preparation</i>		
Cytoplasm	Greenish yellow smooth and hyaline	Yellowish brown granular
Chromatoid bodies	Indistinct	Not visible
Nuclei	1 to 4 (rarely 8) minute central karyosome	1 to 8 (rarely 16 or more), karyosome large and eccentric
Glycogen mass	Yellowish-brown diffuse	Dark brown diffuse with indistinct outline

\* Some strains of *E. coli* have been known to ingest red cells in culture if these are introduced into the medium

The only other finding to which — — — — — presence of Charcot-Leyden cells that there is a high degree of in stools, but they are not diagnostic.

**Complement fixation test**—It is claimed that a 90-per-cent correct diagnosis can be made by means of complement fixation technique with an *E. histolytica* culture extract as the antigen. The results obtained by this test are not entirely consistent, and its specificity is not accepted by all workers.

**Other methods**—Some — — — — — appearance of specimen may examination of the whole, x-rays are not very helpful in an acute or sub acute dysenteric attack.

## TREATMENT

**Historical**—Ipecacuanha has been used in the treatment of dysentery for centuries, it was certainly used in India in 1660. But at this time it was usually given in small doses. In 1846 Parkes revived the interest in this drug and gave it in large doses. In 1866 Macnamara gave the alkaloid emetine that had been isolated from ipecacuanha by Pellether in 1817, by mouth and from the year 1886 ipecacuanha was given regularly in hepatitis. The emetic properties of emetine were recognized and ipecacuanha sine emetine had a short vogue (Neubert 1913), but in 1912 Vedder showed that it was the emetine that killed the amoeba and that the efficacy of ipecacuanha depended on its emetine content.

In 1912 Rogers demonstrated that emetine could be injected subcutaneously and that it acted as a specific in amoebic dysentery and amoebic hepatitis. He standardized the treatment with this valuable drug that has made such a vast difference to the expectation of life of the white soldier in the tropics.

Later work by Dobell and others cast doubt on the specific action of emetine on amoeba *in vivo* and the prevalent opinion is that its action is indirect.

Emetine bismuth iodide (EBI) an emetine compound which it was possible to administer without causing vomiting was introduced with the idea that a more direct action on the amoeba in the bowel could be obtained by this oral administration of the drug.

*Holarhena anti-dysenterica* (or Lurchi bark) is an ancient Indian remedy for dysentery. Chopra and others have shown that an extract of this bark has a specific action in amoebic dysentery though distinctly less than that of emetine.

Many synthetic drugs have been introduced during the last twenty years *eg.* arsenical preparations such as stovaine and carbarsone (Reed *et al.* 1932) iodine compounds such as yatrien (Mühlens and Menk 1921) and acridine compounds such as rivanol for all of which a specific action on the amoeba is claimed.

**Treatment of the acute attack**—Emetine, one of the most useful and almost certainly the most effective — — — — —

abled, and yet others probably killed, by a course of 12 grains in 12 days (*vide infra*). That is to say, as in the case of most drugs, the personal factor is important and it is essential to play for safety.

Directly a diagnosis of amoebic dysentery has been made, a course of emetine should be started without delay. To an adult, six injections of one grain each should be given during the first six days, after which an interval of three to six days should be allowed and the course repeated, in very mild attacks that respond immediately, three injections in the second course will be sufficient. After this, an interval of at least two weeks should be allowed before any more emetine is given, whatever the circumstances, few cases in which the infection is confined to the bowel will require any further emetine, but the more serious hepatic infections will

For small women and children, the size of the individual dose of emetine should be reduced proportionately

**Routine**—An ounce of castor oil with 15 minims of tincture of opium should be given on the first day followed by one gram of emetine hydrochloride given intramuscularly the patient should be confined strictly to bed and given a light fluid diet mainly consisting of low fat content milk or milk preparation. From the following day or from the evening of the same day, if the castor oil was given early he should be given 2 drachms of bismuth carbonate in a glass of water four-hourly night and day and one grain of emetine intramuscularly 2½ hours after the first daily dose of bismuth. The bismuth may be reduced to thrice daily if the main symptoms—pain and frequent stools—subside and discontinued altogether in these circumstances when the first course of emetine is complete other

being taken a dose of salts should be given to ensure complete evacuation of the drug as otherwise its action is likely to be cumulative. Or for this immediate follow up course emetine bismuth iodide (EBI) is favoured by some workers. This is given in 3 grain doses for a week to ten days in hard gelatin capsules or as salol-coated pills taken at night two hours after necessary by some sedative mixture opium 15 minims. These precau-

can be rounded off by prescribing

of the sigmoidoscope

The vast majority of cases will respond to this course of treatment. Those who do not must be looked upon as chronic cases and treated accordingly (*vide infra*)

**Diet**—As stated above at first the diet must be light and fluid lime  
finger's food fruit  
light solids milk  
food with much  
semi vegetarian  
dietary which does not contain too much roughage should be maintained for some time, this tends to keep the large bowel content alkaline

**Toxic effects of emetine**—The ill advised administration of and serious on account of the who are being poisoned. During of inexperienced medical officer daily for long periods and later often quite unaware on account of the frequent evacuations from hospital that are inevitable in war time. In the subsequent years he has seen athletic young men's hearts disorganized for years through the failure of their medical advisers to realize that they should advocate strict rest in bed during the whole time  
his it produces  
with a fall of  
result of any  
undue effort. It also may cause acute mental depression neuritis myositis

changes in the skin and nails, and diarrhoea, which last named is likely to be attributed to the dysenteric condition

#### Other symptoms

rest at night  
or so until the  
aided by hot applications of turpentine stupes

Tenesmus is less common but can be relieved in the same way as in bacillary dysentery (*vide supra*)

**Treatment of chronic amoebic dysentery**—This presents one of the major problems of tropical medicine. The action of emetine is specific if given early, and every effort should be made to give an efficient course in good time. However, in the chronic stages, the action of emetine is very disappointing, and in the absence of hepatitis, it is questionable if it should be employed at all.

At this stage, drugs that have a direct action on the intestinal mucosa appear to act better than emetine, and therefore emetine bismuth iodide, given as indicated above, is of value. However, in the writer's experience, carbarsone is the most useful drug at this stage, provided that there is no hepatitis or cirrhosis, other drugs, such as chiniofon, diodoquin, vioform and their special advocates, and it may be an obstinate case, but even then a curative bowel washes are also given.

Chiniofon (yatren) is given in doses of (about 4 grains) 4

increased to two p  
if it can be tolerated, for ten days

Vioform, also best given in the form of keratin-coated capsules and diodoquin are given in doses of 0.63 gramme three or four times a day. In the case of the former, it is best to limit the course to 10 days, as toxic effects have been reported, but the latter can be continued safely up to a full three weeks.

For medicated bowel washes, chiniofon (20 ccm of a 2.5 per cent solution) is the most popular, and considerable success has been claimed with it by some workers, although the writer has been less fortunate. Manson Bahr (1939) uses a combination of EBI by mouth and chiniofon per rectum, which he claims is almost infallible.

Other bowel medicaments have been used with success, *eg* rivanol which is recommended in a strength of 1 in 2000, but the writer has usually found that silver nitrate solution combined with the administration by mouth of some 'specific' drug, *eg* carbarsone, is as good as the far more expensive yatren.

All medicated bowel washes must be preceded by a 2 per cent sodium bicarbonate enema, which the patient retains for about 10 minutes and then passes as completely as possible. After this, the medicated retention-enema is run in slowly—about 8 ounces is usually sufficient for the patient to retain comfortably, he should retain this as long as possible, up to 8 hours in the case of yatren (2.5 per cent). Silver nitrate is given in increasing strength, from 1 in 750 up to 1 in 250 or even stronger. If the enema causes much pain, it can be washed out immediately with normal saline, but if not, it should be retained as long as possible, up to about 5 hours. The patient should lie on his left side whilst the wash is being run in, and should then assume the knee elbow position to allow it to run well up into the transverse colon and, one hopes, beyond.

It is usually necessary to keep up the bowel washes for at least a fortnight before much benefit will be apparent, except some soothing effect.

which is often an almost immediate result and they may have to be continued daily for a month or more. Later, as improvement is established, the washes may be reduced to one every other day.

After this course, extract of kurchi and ispaghula (*vide supra*) should be prescribed for at least two months.

**Vaccines**—In chronic ulcers, which are mainly maintained by secondary infection, but in which the amoebæ are still active, a vaccine preferably made from an organism obtained directly from the ulcer by means of the sigmoidoscope, is sometimes helpful (*see p 412*). When the secondary bacterial infection is overcome, the tissues are apparently better able to deal with the amoebic infection.

**Diet**—Great care must be exercised in advising patients about their

..

As secondary infection of the ulcers is an important factor at this stage, it may be useful to attempt to influence the intestinal flora by giving bulgarized milk (in India the ordinary dahi will serve the same purpose), with or without the addition of lactose, a heaped tablespoonful first thing in the morning.

## PREVENTION

Man is apparently the sole source of infection so that proper faecal disposal and sewage treatment are the most important measures. It should be remembered that the cysts—the infective form—will survive in a septic tank for some months.

Water is not usually incriminated—although it was the vehicle in at least two historic epidemics, however, it cannot be ignored as ordinary chemical methods of water sterilization will not destroy cysts although almost any form of filtration will. The writer believes that more attention

value as a preventive measure, as such persons pass few cysts, it is important however that, when they become convalescent, they should be followed, examined periodically, and, if they are found to be passing cysts treated.

Most of the measures for prevention are thus general sanitary measures, and the only special preventive measure is with reference to carriers (*quod vide*). In institutions and households a systematic stool examination should be carried out amongst all food handlers and the 'carriers' weeded out and treated. What is at present impeding legislation in the matter of enforcing such precautions in public eating places is the uncertainty regarding the importance of the 'cyst passer' in temperate

countries, but the measure should be rigidly enforced in the case of the convalescent carrier, especially in tropical countries

### PROGNOSIS

This will depend on how soon treatment is undertaken and on its efficacy. It is impossible to give figures, but an initial attack is very rarely fulminant. Almost all the deaths that occur as a direct or indirect result of amoebic dysentery are due to neglect of treatment in the early stages. There is however a small percentage of cases in which the symptoms persist for months and even years, despite (ordinarily) efficient measures.

With the establishment of hepatic complications the prognosis becomes graver (*vide infra*).

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PLATE XII (Cysts)



13



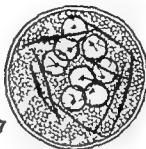
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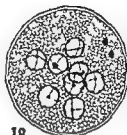
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VEDDER E H (1912)

An experimental Study of the Action of  
Ipecacuanha on Amœbæ *Trans Second*  
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Experimental Entamoebæ Dysentery *Philippine J Sci* ■ 253

## The Iron-hæmatoxylin Staining Method\*

The accurate differentiation of *Entamoeba histolytica* from other amœbæ and cysts requires experience. In most cases an identification can

anyone who wishes to learn to identify amœbæ to use the iron hæmatoxylin

MISSION

ing by  
roces  
ly and

Leave

- in 3 minutes  
3 Transfer to 70% alcohol for 2 minutes  
4 Transfer to 70% iodine alcohol for 2 minutes. This is prepared by add  
ing sufficient tincture of iodine to the alcohol to give a dark amber  
color

1

1

1

13

14

- 15 Place in xylol for 2 minutes  
16 Mount in balsam or gum damar using a No 1 cover glass. In place of  
step 14 two changes of dioxane may be used for dehydration

\*<sup>1</sup> *Schaudinn's Fixing Fluid*. Distilled water saturated with mercuric chloride 2 parts 95% alcohol 1 part. Add 5 to 10 cc of glacial acetic acid to every 100 cc of this mixture

<sup>2</sup> *Iron Alum*. 2% aqueous solution of ammonium ferric sulfate

<sup>3</sup> *Hematoxylin Stain*. 0.5% aqueous solution of alcoholic ripened stain. Stain solution is prepared by dissolving one part of hæmatoxylin crystals in 10 parts of absolute alcohol. This may be ripened in one of several ways

- 1 By the ordinary slow process of standing for several months
- 2 By placing in an incubator for two weeks
- 3 By adding hydrogen peroxide
- 4 By adding carbolic acid and then boiling

The ripened stain should be diluted to 0.5% by adding distilled water. If upon using the stain is found to be insufficiently ripened a few drops of hydrogen peroxide or of carbolic acid should be added to each 100 cc of solution and the solution heated

periods of reactivation and advance. At this stage also, emetine will often control the condition, but it must be given for a longer time.

The stage of liver abscess will usually present a more definite clinical picture, but nevertheless there are many cases that show few or none of the classical signs and symptoms, and cases are on record in which an abscess has suddenly burst, *e.g.* into the lung, without any previous record of ill health.

The patient may give a history of previous illness that would corre-

have a grey look with a sub-icteric tinting of the skin and sclerotics, but

of fever develop  
nt occa-  
ugh con-  
ng His  
plam of  
dysphagia indigestion severe liver pain, which  
is usually stabbing in nature and very often  
referred to the right shoulder, and an irritable  
cough. The leucocyte count will be 20,000 per  
c mm or more but this is not a constant find-  
ing (see figure 130), and a normal or a lower

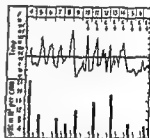


Figure 130 Shows the leucostancy of the leucocytosis in liver abscess the condition responded to emetine treatment

be caused when the thorax over the liver area is pressed between the hands, there will also be tenderness in the intercostal spaces, and there may be some intercostal oedema.

Other physical signs will depend on the size and position of the abscess. If it is in the left lobe or in the palpable portion of the liver below the costal arch, it may produce a local bulge in the abdominal wall which it is possible to recognize as an abscess, it may be tense, but it is more usually soft and can be distinguished from a hydatid cyst by the absence of

There will often be tenderness in the right lung

The abscess may point and eventually rupture externally, internally through the chest wall, or below the costal margin, or it may

ruptures into the lung, the contents are immediately coughed out, and the patient may die of dyspnoea, or of shock, but, if he recovers from the immediate effects, complete recovery is very common. The walls of the abscess collapse and close the opening and sepsis may be obviated

PLATE XIII  
*Amœbic liver abscess*



Fig 1.—Showing the high raised right dome of the diaphragm it has an unusually clean cut outline. The heart is pushed over to the left. Two pints of pus were obtained by aspiration.



Fig 2.—Showing a local dome-shaped swelling superimposed on the right dome.

PLATE XIV  
*Amœbic liver abscess*

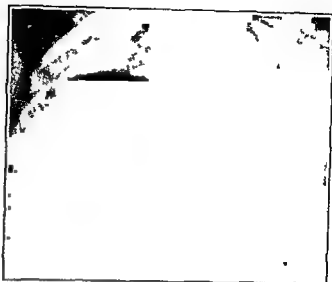


FIG 3—Showing another high right dome

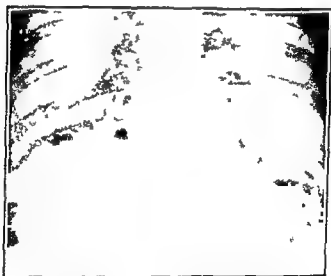


FIG 4—In this case the diaphragm is scarcely raised but the lung is apparently involved. Two days before this was taken the patient coughed up over a pint of pus. He made an uninterrupted recovery.

Rupture into the pleural cavity is far less common. Other common directions are into one of the hollow viscera stomach, duodenum or large intestine. Rupture into the pericardium, the gall bladder the pelvis of the kidney or into the loose perinephric tissue, and into the peritoneal cavity has been reported (see figure 131)

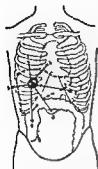


Figure 131 Diagram showing some of the directions in which a liver abscess may burst

- 1 Into the lung or pleural cavity
- 2 Into the stomach
- 3 Into the duodenum
- 4 Into the cecum
- 5 Through the skin
- 6 Into the pericardium

**Diagnosis**—If the patient gives a history of living in the tropics under conditions in which he is likely to have acquired an amœbic infection not too much attention should be paid to whether he has actually suffered from amœbic

the therapeutic test with emetine is of value in the early stage of simple hepatitis, a definite response will usually follow three daily injections, if it is suspected that the stage of milary abscesses has been reached at least six should be given and even when there is a large abscess, some distinct clinical improvement will usually follow six injections but it may be advisable to persist up to nine. The blood picture will give additional evidence but it must be remembered that the leucocytosis is neither as constant nor as high as one might expect. The final court in the diagnosis of liver abscess is an exploratory puncture.

**Technique of exploratory puncture**—A large serum syringe with a needle of moderate bore (about no 9) not less than 3½ inches long is used. A local anæsthetic should be injected at the point selected. The needle is inserted either at a point where the abscess appears to be pointing or when there is no such indication in the 8th interspace in the mid axillary line and thrust into the liver substance at first in a slightly upward and forward direction towards the right cupola of the diaphragm if no pus is obtained the needle is partly withdrawn and pushed in again in another direction a third or even a fourth attempt may be made but if these fail it must be assumed that there is no large abscess present. If the anatomy of the liver is visualized if common sense is used and if care is taken to avoid the gall bladder and not to thrust the needle in to a depth greater than 3½ inches in any direction the

aspirated *vide infra*)

**Differential diagnosis**—In view of the very considerable variability in the signs and symptoms of amœbic hepatitis and liver abscess, and the possible absence of any especially in the early stages, an adequate discussion on this subject would cover half the field of internal medicine. In

these circumstances, it will be best to give a short classification, with a few examples, of the diseases that may simulate, or be simulated by, amoebic hepatitis and liver abscess

**Febrile conditions** **Long fevers**—Typhoid, tuberculous, and *Bacillus coli* infections, the Pel-Ebstein syndrome, undulant fever, and kala azar

**Short fevers**—Malaria, relapsing fever, rat-bite fever, and leptospirosis

In most of these conditions either rigors or profuse sweating will sometimes if not usually, occur, and either of these symptoms will heighten the similarity

*Hepatic conditions, such as cirrhosis, syphilis, gumma, carcinoma, and pyæmic abscesses*

**Extra hepatic conditions**—Pneumonia, basal pleurisy and empyema, cholecystitis and suppurative cholangitis, pyelonephritis, perinephric abscess, and sub-phrenic abscess, appendicitis with complications

TREATMENT

**General**—The patient must be confined to bed whenever a definite He should be given the febrile bouts,

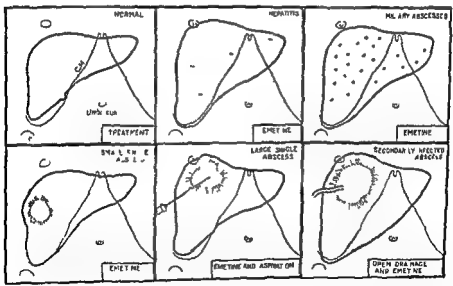


Figure 132 Showing five stages of liver involvement and the treatment of choice in each case

Local applications, hot fomentation or antile and aspirin phenobarbi-

with magnesium sulphate, liquorice powder, or a mercury and aloes pill (see p 51)

In severe cases, a daily dose of intravenous glucose will be beneficial

**Specific**—It is in the hepatic complications of amoebic dysentery that emetine is of the greatest value, and, in amoebic liver abscess, the combined

treatment of emetine administration with aspiration is a very great advance on the previous method of open operation in which the death rate was always above 40 per cent.

At every stage of the invasion of the liver by amœbæ, emetine is of value. Some indication has already been given of what may be expected from emetine administration.

While in the earliest stage of hepatitis, three one-grain injections will

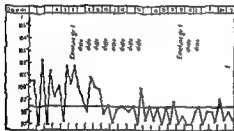


Figure 133 Showing a rapid response to emetine, the process had probably reached only the military-abscess stage

already been given and if the urgency of the occasion seems to permit, it should be given before the operation, if not, then after operation, until the fever is controlled or 12 injections have been given. In a serious condition like this certain risks (see p. 439), which might be unjustifiable in other circumstances, have to be taken with emetine dosage (e.g. cases of figures 134 and 135).

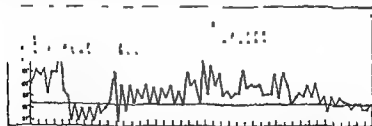


Figure 134 Showing delayed response to an 'overdose' of emetine (see text)

In the case of which the temperature chart is shown (figure 134), aspiration was seriously contemplated as his temperature had not fallen after 12 emetine injections, but instead emetine was given again, and aspiration obviated. In another case (figure 135) both aspiration and emetine were necessary, but the

**Aspiration**—Even when a large abscess has obviously formed, it is quite often possible to control the condition by emetine alone without aspiration. However, if the evidence points to a large abscess, or if preliminary treatment, while perhaps controlling the fever to some extent, has obviously not completely halted the pathological process, it will be as well not to postpone aspiration any longer. If emetine has not



After the abscess has been aspirated, if the fever continues, it may be advisable to give further emetine injections. The risk of giving these may have to be weighed against the risk of allowing the pathological process in the liver to extend. Eventually, even in an uninfected abscess, the time may come when open drainage will have to be considered, but this should be postponed as long as possible, for once a drainage tube is put in, contamination is inevitable.

secondary infected open drainage  
if the surgeon,  
be mentioned

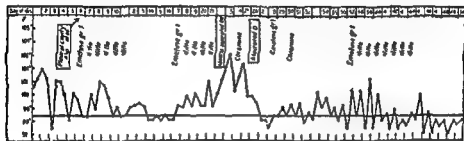


Figure 135 This was a very bad case two liver and one pleural aspirations were required as well as 20 grains of emetine

**Prevention**—Basically the prevention of liver abscess is the prevention of amoebic infection. There appears to be no danger of liver abscess developing in the intestinal amoebic infections that occur in temperate climates, but in a tropical country such an infection must be looked upon as a potential danger, and certainly in all cases in which there is frank

amoebiasis. Emetine appears (vide supra) to be the consummational amoebiasis, re, and has no

as in poor, the sometimes reported as

70 per cent—in pre-emetine days

In amoebic hepatitis, by efficient treatment, it should be possible to prevent abscess formation in every case, but later, when an abscess has developed, the death rate is still from 10 to 15 per cent

## OTHER PROTOZOAL AND METAZOAL DYSENTERIES AND DIARRHŒAS

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### FLAGELLATE DIARRHŒAS      GIARDIASIS

**Discussion**—The commonest intestinal flagellates are *Trichomonas intestinalis* and *Chilomastix mesnili* which infest the cæcum and large intestine and *Giardia enterica* (*Giardia intestinalis* or *lamblia*) which is

this does not mean that the flagellates cause this condition on the contrary the condition of the bowel probably encourages the flagellates to



which he does not believe exists he will make no further reference to the other flagellates and will discuss only giardiasis

**Historical**—Leeuwenhoek discovered the parasite whilst using his primitive microscope in 1681. It was rediscovered as a human parasite by Lambl in 1859 and given the name *Lamblia intestinalis* but as another species of the genus had previously been described and given the generic name *Giardia* Lambl's parasite

was renamed *Giardia intestinalis*. It was later pointed out that the specific name *intestinalis* was already occupied and that the correct name is *Giardia enterica*. The name *Giardia lamblia* is also used, but is not in accordance with the rules of nomenclature.

**Epidemiology**—Giardiasis occurs in all countries, but is probably more common in the tropics. It is found in persons of all ages, but it produces more definite symptoms in children than in adults. It was found in 6.27 per cent of about 20,000 stool samples from a mixed population examined in Calcutta between 1935 and 1938. In children, the general infection rate is higher.

There appears to be no reason for attributing any racial predilection to this infection, and, although the incidence is to some extent inversely

the highest infection rate have acquired any tolerance to the ill-effects of the infection, the writer has frequently seen symptomatic giardiasis in such persons.

**Ætiology and pathology**—*Giardia enterica* is a flagellate parasite with a trophozoite and a cystic stage. The former is pear-shaped and dorsally convex, it has a 'sucking disc' in its ventral concavity, and four pairs of flagella, it has a colourless granular cytoplasm, and two nuclei (not seen in the unstained specimen), in size it varies from 10 to 20 $\mu$  in length and from 5 to 15 $\mu$  in breadth, it is actively motile in the freshly passed fluid stool, but soon loses its flagella and motility in a formed or stale stool. The cysts are oval, 8 to 12 $\mu$  in length and 7 to 10 $\mu$  in breadth, they are colourless, and have four nuclei and a well defined cyst wall.

The parasite lives and multiplies in the intestinal tract, from the duodenum to the caecum. Both the cysts and the trophozoites are found in

that they affect the function of the intestinal mucosa which they excess of mucus. It is also very probable the mucous membrane and interfere with the attachment of Giardia infestation, responsible for enteritis.

treatment, and one is naturally inclined to attribute the lack of clinical effects to the fact that the parasite is not present in the small intestine. However, it is quite obvious that there are many persons with giardia infection, who suffer no recognizable ill effects.

The most constant symptoms are (a) diarrhoea—the stools are usually loose and watery, but may be definitely fatty, (b) abdominal pain or discomfort, either <sup>not often associated</sup> with flatulence and sometimes with loss of appetite, or in the lower segment by defecation, and (c) irregular fever.

(c) irregular fever  
Children also are usually irritable and tiresome, and develop capriciousness, - recognized as being  
have shown  
sore tongue,  
of total fat  
nce of all the

In addition, adult patients often feel definitely ill and weak, and they may exhibit nervous symptoms, such as irritability and anxiety.

Abdominal tenderness is constant in the cases with symptoms, this is usually in the epigastrium, but sometimes in the region of the cæcum.

**Treatment**—Of the innumerable treatments advocated none proved really successful until Brumpt (1937) and Martin (1937) introduced mepacrine (atebrin), which appears to be a specific.

A large percentage of complete cures will be achieved with a course of 0.1 gramme three times a day for five days. Children should be given smaller doses (see p. 101). A second course after an interval of about a week will be necessary in a few cases. If there is any doubt about the cure it is advisable to give this second course.

### CILIATE DYSENTERY BALANTIDIASIS

Although balantidiasis is a rare infection there seems no possible question that it occurs and may be serious. Some 250 cases have been recorded.

It is reported from North America, and several from South America and Africa. It is universal in the tropics, and common in the Indian and Chinese countries. Two cases have been reported from the United States.



Figure 137 *Balantidium coli*

**Occupational incidence**—It occurs in swineherds and pork-butchers and other persons closely associated with pigs.

**Ætiology**—*Balantidium coli* is a ciliate protozoa, a natural parasite of pigs, to which it appears to do little harm. It is transmitted to man apparently by food contamination. Experimentally it is transmitted with great difficulty.

**Pathology**—The parasites invade the mucosa of the large intestine apparently in exactly the same way as does *Entamoeba*.

*histolytica*. The ileum has also been involved. Entering the crypts of Lieberkuhn, the parasites secrete a kind of cytotoxin, and penetrate into the submucosa, and thence even into the intestinal lymph nodes. The ulceration produced is similar to that of amœbic dysentery. Perforation has been reported.

**Symptomatology**—This is again indistinguishable from that of amœbic dysentery. The onset is often very insidious but the condition may develop seriously, and it is usually very persistent. Anæmia is a marked feature and later cachexia develops.

**Diagnosis** will be made only by finding the *Balantidium coli* in the stool. It is a large parasite easily seen with the low-power lens.

**Treatment**—This has not been very satisfactory. Large (dangerous) doses of emetine, gr 1 daily for 15 to 20 days, have produced a cure in a number of cases, and recently methylene blue—administered by mouth in

2-grain pills and as an enema in a strength of 1 in 3,000—has been used with some success. Drachm doses of carbon tetrachloride have also been used successfully.

**Prognosis**—A number of deaths have been reported. The mortality can be placed at between 10 and 20 per cent.

In some cases, the infection has persisted for from four to fifteen years.

### COCCIDIOSIS

Infections with the coccidium, *Isospora hominis*, are not rare in the tropics and sub-tropics, and are usually associated with sub-acute dysenteric symptoms.



Figure 138. *Isospora hominis*

(Dobell and O'Connor 1921)

- 1 Oocyst with unsegmented protoplasm, as usually passed in stools
- 2 Later stage, nucleus divided into two
- 3 Fully developed oocyst containing two spores—each containing four sporozoites
- 4 Degenerate oocysts which have failed to develop

**Epidemiology**—The infection has been reported in most countries in the tropics and sub-tropics, but rarely in the temperate zones. The apparently greater frequency in the Mediterranean area probably reflects only the fact that greater attention has been paid to it there. In routine stool examinations in India, it is not such a rare finding that observers think it necessary to report each case. Nine cases have been encountered in the last twenty years at the Calcutta School of Tropical Medicine (Das Gupta 1934).

The majority of the infections reported have apparently been in adults.

**Ætiology and pathology**—The parasite, *Isospora hominis*, infests the small intestine and invades the mucosa. The oocysts, which are found

Infection of man takes place in the oocyst stage by the oral route.

**Symptomatology**—Symptomless infections are not uncommon. Infection is usually associated with mild chronic diarrhoeal symptoms, some malaise and mental depression, loss of appetite and weight, and occasionally epigastric discomfort.

The stools are light-coloured, contain much undigested food, and show a tendency to be fatty.

**Diagnosis** can be made only by finding the oocysts in the stools. The only other characteristic finding, which is almost constant, is Charcot-Leyden crystals.

**Treatment**—No entirely satisfactory treatment has been found.

1 of a the most successful procedures

are those of the important

syndrome caused by these parasites is discussed. Diarrhoeal symptoms have been associated with two other trematodes, *Fasciolopsis buski* and *Heterophyes heterophyes*, and two nematodes, *Esophagostomum apistomum*

a catarrhal condition of the gut which leads to diarrhoea, pain in the abdomen, œdema and ascites, and a serious condition of ill-health, which develops gradually.

Most antihelminthic drugs will effect a cure, e.g. carbon tetrachloride or tetrachlorethylene given in doses of 3 or 4 ccm with the usual precautions.

*Heterophyes heterophyes* infests dogs, cats and other carnivores and man. They similarly develop in snails, the cercariae are ingested by fish, and man becomes infected by eating insufficiently cooked fish.

If present in the small intestine in large number, they also produce a catarrhal condition of the mucous membrane. The clinical picture is similar to that associated with *Fasciolopsis* infection.

In the treatment of this infection, most of the ordinary anthelmintics have been tried, usually with good effect.

Nematode diarrhoeas and dysenteries—*Esophagostomum apistomum* is a common nematode in monkeys in West Africa, and it occurs also in Asia, it has not been reported in India. The larvae are swallowed, and reach the cæcum where they bury themselves in the mucous membrane, and develop. The nodule thus formed bursts into the lumen of the cæcum, and the worm attaches itself to the mucous membrane. Secondary infection worms themselves may be either

probably other anthelmintics would prove as satisfactory.

*Strongyloides stercoralis*, to which further reference will be made, also causes a diarrhoea.

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# CHRONIC POST-DYSENTERIC ULCERATIVE COLITIS

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**Discussion**—Ulcerative colitis is not an exclusively tropical condition, and in fact has received far more attention in cosmopolitan medical literature than in that section of medical literature that deals mainly with tropical diseases. There has been much inconclusive discussion on the ætiology of so called idiopathic ulcerative colitis; we are little concerned with this for whether or not bacillary dysentery is a common cause of the ulcerative colitis of temperate countries, certainly a chronic ulcerative colitis is not an uncommon sequel to both bacillary and amœbic dysentery in the  
mœbic  
exists  
t least

**Ætiology**—As has been indicated above the condition we are considering here is not *now* maintained by either *Entamœba histolytica* or one of the recognized dysentery bacilli; and the finding of a small number of organisms of either of these genera in the stools does not necessarily indicate that the main pathological process is maintained by them. For

independent of a chronic ulcerative condition of the bowel, commonly a 'carrier' type of amœbic infection may exist in one part of the gut when elsewhere there is a non specific ulceration

The principal micro organism that is now maintaining the pathological process will probably vary from case to case. Streptococci are usually recovered most readily from the ulcers but there is still much work to be done on the identification and classification of the flora of these ulcers.

Cultures from the stools may be misleading and the true culprit is likely to be identified only by taking swabs directly from the ulcers after colonic lavage with the aid of the sigmoidoscope. Bacterium diplococcus which it is claimed is frequently present in the idiopathic form has seldom been identified in the tropics.

The main predisposing factor is of course the damage done to the gut mucous membrane and deeper structures during the primary (specific) ulceration. It is not difficult to understand how such large denuded areas fail to heal whilst in more or less continuous contact with the septic gut contents. However as we know that healing does frequently occur we

even in the well to do patient from long periods of restricted diet

### PATHOLOGY

The ulcers may be in any part of the colon but are usually in the sigmoid or rectum. The caecum is the next most common site. The ulcers are usually oval in shape but may be serpiginous. The edge may have a clean cut punched out appearance or it may be rounded hard and fibrous it very rarely if ever shows the irregular undermined edge of the extending ulcer. The mucous membrane in the areas between the ulcers is usually healthy.

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lumen. More  
mucous mem

brane with polypoid formations

**Blood**—There is no characteristic blood picture. There are two influences the tendency to microcytic anaemia as a result of repeated blood loss from the ulcers which may become an important factor and the tendency to a nutritional anaemia as a result of dietary restriction. However in the uncomplicated condition may be almost normal. There is

### SYMPTOMATOLOGY

**Clinical history**—The condition is usually of the type of dysentery but more frequently most of which may have been recurrent they were inadequately treated sufficient importance to them or occurred

The onset may however be entirely spontaneous and without any previous history of bowel disorder.

**Symptoms**—When the condition is fully established the patient will complain of more or less continuous discomfort in the abdomen which is less insistent after a period of rest and dietary restriction and is increased





giving by mouth some of the recognized arsenic or iodine preparations used in the treatment of amoebic dysentery (*qv*), and recently we have had

**Colonic irrigation**—Many drugs have been recommended eusol, chiniofon vioform sodium sulphapyridine and several organic silver preparations but the writer has found silver nitrate as satisfactory as any of these more expensive drugs.

bowel washes should be run in through a soft catheter under low pressure (18 inches to two feet of water)

the solution should be 1 in 1000 at first stages to 1 in 750 1 in 500 1 in 400

If on any particular day the enema is not effective it with normal saline

The patient should be encouraged to retain the medicated enema as long as possible up to five hours. These washes should be given daily or if the symptoms are severe

free diet by rapid stages. The diet must contain adequate protein in some easily digestible form and all the vitamins and minerals but it must include only the minimum of residue. Plenty of fluid and adequate salt.

**G**  
by mouth  
possible  
laxatives should be taken

The anaemia should be treated with suitable haematinics as indicated by the blood counts but very often it will be advisable to give both liver and iron. In severe cases a blood transfusion will often initiate a period of improvement. Sedatives analgesics and antispasmodics may be required. It may be advisable to give a bromide mixture for a week or so at the outset and at night in order to ensure a good night's sleep. The latter in the form of D.

**Progress**—Except

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treatment too soon even after an apparent complete cure a relapse is very liable to occur unless great care is taken regarding the diet in particular, for months or even years.

On the other hand, if the patient does not improve after two or three months' treatment, and after several changes of bowel wash, surgical treatment will have to be considered. Two operations are recommended, appendicostomy and ileostomy, by the former, a means of giving efficient bowel washes is provided, and by the latter the faecal matter from the upper bowel is side-tracked as well. The latter is undoubtedly more efficient, but the former is simpler to do, and much simpler to undo when it is no longer required. Care should be taken not to resort to surgery too late, because once the large intestine has become fibrotic, it will contract with disuse, and become a hard narrow tube that will never function again properly, and a permanent colostomy will be the result.

**Prognosis**—This will depend on how early the treatment is undertaken, and on the vigour and skill with which it is prosecuted, this in turn will depend on the co-operation of the patient, and on the circumstances in which he is placed.

If proper treatment is undertaken early, cure should always be possible, but many neglected patients have passed into a stage of chronic invalidism, while others have gone rapidly downhill, and have died of exhaustion or intercurrent disease within a few months.

**Addendum**—Stannus (1943)\* has developed a very attractive theory on the aetiology of sprue. He considers that the primary physiological lesion in sprue is a defect of the small intestine, and that this is determined by a defect in the autonomic nervous system. This defect he believes to be a complex possibly including

The present writer's hypothesis that behind the aetiology of sprue there is an inborn error or 'weakness' of metabolism seems to tie in well with Dr Stannus's hypothesis except that in the former there is less emphasis on the specific dietary deficiency and more on the constitutional factor.

\* Stannus H S (1943) *Sprue*. *Trans Roy Soc Trop Med & Hyg* 36 123

# SPRUE

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**Introduction** —Most of the early writers on sprue emphasized the fact that the disease was confined to Europeans or persons of mixed European and Asiatic descent. It has long been recognized that the incidence in different racial groups is in inverse ratio to the degree of pigmentation of their skins. There is, however, a natural tendency to report the rare case, so that the exceptional cases of sprue in Indians or other indigenous inhabitants of the tropics have received greater publicity than the ordinary run of cases in Europeans, with the natural consequence that the undoubted fact that typical cases do occur amongst Europeans has not yet seen a typical case of that typical cases do occur amongst

There occurs, however, commonly amongst Indians a now-well-recognized syndrome of macrocytic anaemia, nutritional in origin, that is often associated with a chronic watery diarrhoea. In some of these cases, there are certain signs and symptoms that are also typical features of the sprue syndrome, for example, emaciation and a sore, red and glazed tongue. In fact many of these cases in Indians would pass as modified sprue, and are often diagnosed as such.

There is also a condition of chronic watery diarrhoea, with perhaps a slightly sore tongue but at first without macrocytic anaemia, that occurs amongst both Europeans and Indians and is usually referred to as 'pre-sprue'. The name is not a good one, as, even if one does not take the view that true sprue never occurs in Indians, the name implies that sprue must inevitably follow unless the condition is cured. This is not the case, for, although many patients with sprue give a history of previous diarrhoea, this diarrhoeal condition referred to here may continue for many months and even years without the patient's developing further typical symptoms of sprue, but emaciation, a sore tongue and a macrocytic anaemia are common sequelae, so that the condition develops into the malnutritional syndrome described above as commonly occurring in Indians. For this condition the writer has for some years used the word 'para-sprue'.

While there are undoubtedly all degrees of conditions between (a) nutritional macrocytic anaemia, with or without diarrhoea, (b) para-sprue, and (c) true sprue, the writer believes that they are not just stages of the same condition, but that para-sprue and sprue have different aetiologies, just as they have distinguishable clinical pictures. The conditions are therefore described separately.

**Definition** —Sprue, or psilosis, is a diarrhoeal condition of uncertain aetiology, characterized by emaciation, the passage of large, light-coloured and frothy stools with a high fat content, flatulent dyspepsia, a sore tongue, a low glucose tolerance curve, and eventually a marked macrocytic anaemia occurring amongst people who live, or have lived, in certain tropical countries.

**Historical** —Early historical records of this still not very clear-cut syndrome are not very clear and it is obvious that many refer to other diarrhoeal diseases. Manson B refers to Ketelsaer in 1669 and of Hillary in 1877. The name was first used in the descriptions of sprue in Java in 1879 and 1880 respectively.

Recent contributions to our knowledge of this disease have been more destructive than constructive for example Thaysen (1931) and later Mackie and Fairley (1934) showed that our previous conception of the morbid anatomy of the disease was entirely erroneous.

## EPIDEMIOLOGY

**Geographical distribution** —'Sprue' without any qualification usually refers to 'tropical sprue' but there is little question that there is an indis-

tinguishable condition which occurs amongst persons who have lived all their lives in a temperate climate, to this the name 'non-tropical sprue' is usually given. Some 170 cases of non tropical sprue have been described, these reports have come from several countries, mainly the U.S.A. and Great Britain.

Tropical spruce is most commonly associated with residence in China, India, Ceylon, Malaya, the East and West Indies, southern USA, Central and South America, southern Italy, and Queensland, that is to say it is for the most part truly tropical, but a few sub-tropical areas are included, and the disease is rare in tropical Africa. Its realm lies between 40°N and 20°S.

**Age and sex**—It is more common in females than males, and is essentially a disease of middle age, but it may occur in young people and even in children.

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attacks of hilly diarrhoea

**Seasonal**—The onset is usually after or during the rains

**Other epidemiological observations**—Sprue houses in which a succession of residents have suffered from sprue have been reported, and this has led to theories regarding its infectious nature also, husband and wife not infrequently both suffer from the disease. It has been specifically associated with heavy white-ant infestation of the house and with dry rot, neither being very unusual associations in the tropics.

**Time relation to tropical residence**—It is usually associated with long tropical residence and it is common in the domiciled European in tropical

sojourn  
this has  
means u

## ÆTIOLOGY

- (i) Syphilis has a definite incubation period of usually three to six months after residence in the tropics
- (ii) The geographical distribution is patchy and peculiar
- (iii) Evidence has been collected that several members of the same family

[illegible]



provement in the blood picture and also in the general condition, but even in the cases in which anemia is the most prominent symptom, this treatment alone is seldom sufficient. Those reported cases in which liver treatment alone was effective were probably not true sprue but para sprue nutritional macrocytic anemia.

### Diets

**Rationale**—The object of the dietary is to rest the disorganized fat and carbohydrate digestive mechanism and at the same time to ensure proper nutrition to the tissues. This is best done by giving a high protein diet with a sufficiency of all the vitamins and essential minerals and at the same time restricting the fat and carbohydrate intake.

If this principle is observed the details are not of very great importance and the diet will certainly have to be varied according to the circumstances under which the patients are being treated as well as from patient to patient.

The ratio of protein fat carbohydrate in a normal diet is 1 : 1 : 5. In a sprue diet, the proportions of fat and carbohydrate must each be

1/2, 1/2, 1/2. By very nearly but obtaining

use milk, spru-lac, a proprietary (Cow and Gate) preparation of dried milk with an exceptionally low fat content (P=10 F=0.3 C=13), could be given.

The five stages of this milk diet are given in table X below. The feeds must be taken every two hours from 6 in the morning until 8 at night with an extra milk feed at 2 o'clock in the morning if the patient is awake. This makes 8 milk feeds and one fruit meal the latter in the middle of the day. The milk must not be drunk from a cup but sipped from a spoon at 10, 4, 4, 4, 4.

milk but this difficulty is milk e.g. by peptonization of butter milk or some

TABLE X

Stages	1	2	3	4	5
Milk sk. med. pints	3	4	5	5	4
Whole				1	2
ru l* ounces	8	8	8	8	8
lucose ounces	1	1	1	1 1/2	2
eggs				1	2
butter ounces					1/2
ru l* ounces		1	2	3	3
Calories	846	1166	1490	1956	2412
Proportions					
Proteins	1	1	1	1	1
Fats	0.1	0.1	0.1	0.3	0.5
Carbohydrates	2.2	2.2	2.2	2.3	2.5

\* See footnotes to table XI



Showing the dietary items, their quantity, their protein (P), fat (F) and carbohydrate (C) content, and their calorie value, in the five stages of the sprue diet

## SPRUE

Stages	I			II			III			IV			V		
	Oz	F	Cal	Oz	F	Cal	Oz	P	C	Cal	Oz	P	C	Cal	
Skimmed milk	48	48	5	67	505	60	60	6	84	630	40	40	4	50	420
Whole milk											20	20	2	28	210
Fruit* (orange juice)	8	8	22	96	8	8	8	2	22	96	8	8	2	22	96
Glucose	1	1	30	120	1	1	1	1	45	180	2	2	60	240	2
Chicken						4	34	8	208	208	2	4	4	42	220
Rusk†						1	2	2	110	110	8	24	2	6	138
Liver soup						4	12	1	69	69	4	30	14	246	4
Fish											1	3	3	43	43
Lean meat‡ (beef)											1	3	3	43	43
Egg (boiled)											1	3	3	43	43
Biscuit (plain mild)											1	3	3	43	43
Butter											1	3	3	43	43
Liver (lightly cooked)											1	3	3	43	43
Total	50	5	119	721	110	17	160	1,233	144	23	178	1,495	103	69	2,237
Ratio P F C	10	0.1	2.3	10	0.2	1.4	10	0.2	1.2	10	0.4	1.4	10	0.8	1.4

A cup of weak tea with skimmed milk with glucose (or equivalent amount of sugar) from the ration can be taken once in the second and third times in the fourth and three times in the fifth stages

Notes \* Fruit Orange grape and grape fruit juice and mashed bananas papaya beet fruit and apple have been those most used by us but some other fruits eg strawberries if and when they can be obtained are suitable

† Rusks are bread baked in an oven until crisp one ounce of bread will make about 2/3 ounce of rusk

‡ Meat (beef or mutton) must be lean and raw it should be cut into very thin slices and cooked for not more than one minute in a double saucepan or in a thin frying pan over a saucepan of boiling water The meat becomes light brown colour and loses its raw appearance and taste

If the nurse is preparing the meal it is only necessary for her to place the thin slices of raw meat (or liver) on the plate on which it is to be served and to place the plate over a saucepan of boiling water for about three minutes

The meat as liver can be cut up and eaten or it can be minced in the latter case salt pepper and marmite should be added and if a dry meal is preferred about half an ounce of rusk crumbs (from the ration) should be mixed with the mince

proprietary preparation such as Benger's food bovril added to milk will provide a change

If sprulac is used it must be given as follows —

First stage 6 ounces of sprulac (120 calories to the ounce of dry

added

12 1 1 1 1 1

which is basically of milk, but added will usually be found lines that we have used for eight meals should be taken

during the day and the patient must be given an exact programme to follow

**Meat diet**—The high protein diet recommended by Fairley consists largely of beef good quality beef is difficult to obtain in many tropical countries and further to many patients beef is not only an unpleasant food but does not seem to suit them even if they can be persuaded to take it. However many patients come under treatment in a temperate climate and this diet has certainly been very successful in its originator's hands

Fairley (1939) recommends the following diet —

## TABLE XII

### HIGH PROTEIN MEAT DIET

#### Diet No 1 (calorie value = 770)

8 a.m.—Underdone beef 3 oz rusk  $\frac{1}{2}$  oz juice of  $\frac{1}{2}$  orange and glucose 2 drachms

12 noon—Soup 4 oz + liver extract (=  $\frac{1}{2}$  lb) underdone beef 3 oz rusks  $\frac{1}{2}$  oz juice of  $\frac{1}{2}$  orange and glucose 1 drachm

6 p.m.—The same as at 12 noon

Protein fat carbohydrate = 10 0.3 1.2

*Note*—When patients are very ill two hourly feed of meat and beef juice can be substituted

#### Diet No 2 (calorie value = 1,260)

8 a.m.—Underdone beef 5 oz rusk 1 oz calves-foot jelly 2 oz juice of 1 orange + glucose 2 drachms

12 noon—Soup 4 oz + liver extract (=  $\frac{1}{2}$  lb) underdone beef 5 oz rusks 1 oz juice of 1 orange + glucose 2 drachms

4 p.m.—Tea 10 oz milk 2 oz

7 p.m.—The same as at 12 noon + calves-foot jelly 2 oz

Protein fat carbohydrate = 10 0.3 1.0

#### Diet No 3 (calorie value = 1,620)

8 a.m.—Tea 10 oz milk 2 oz

8 a.m.—Underdone beef 6 oz rusks  $1\frac{1}{2}$  oz calves-foot jelly 2 oz juice of 1 orange + glucose 2 drachms

10 a.m.—1 baked apple custard 1 oz

12 noon—Soup 4 oz + liver extract (=  $\frac{1}{2}$  lb) underdone beef 6 oz calves-foot jelly 2 oz rusks  $1\frac{1}{2}$  oz juice of 1 orange + glucose 2 drachms

4 p.m.—Tea 10 oz milk 2 oz baked apple 1 oz custard 1 oz

7 p.m.—The same as at 12 noon

Protein fat carbohydrate = 10 0.32 1.3

#### Diet No 4 (calorie value = 2,200)

6 a.m.—Tea 10 oz milk 2 oz

8 a.m.—Underdone beef 6 oz rusks 2 oz calves-foot jelly 2 oz juice of

10 a.m.—1 baked apple + custard, 2 oz

12 noon—Soup, 5 oz + liver extract (= 1 lb), underdone beef, 7 oz, calves-foot jelly, 2 oz, rusks, 3 oz, juice of 1 orange + glucose, 2 drachms

4 p.m.—Tea 10 oz, milk, 2 oz, 1 baked apple, custard 3 oz

7 p.m.—The same as at 12 noon, but only 1½ oz of rusks allowed

Protein fat carbohydrate = 10 0.34 13

#### *Diet No 5 (calorie value = 3020)*

6 a.m.—Tea, 10 oz, milk 2 oz, glucose, 2 drachms rusks 1½ oz butter, 1 drachm, one scraped ripe apple or one fully ripe canary banana (yellow ends)

8 a.m.—Underdone beef 7 oz rusks 3 oz, calves foot jelly 2 oz juice of 1 orange + glucose, ½ oz, honey, 2 drachms, butter, 1 drachm

10 a.m.—1 baked apple, custard 3 oz

12 noon—Soup 5 oz + liver extract (= 1 lb), underdone beef, 7 oz, calves-foot jelly, 2 oz, rusks 1½ oz, juice of 1 orange + glucose ½ oz

4 p.m.—Tea 10 oz, milk 2 oz, glucose 2 drachms, rusks 3 oz, baked apple 1 oz, custard 3 oz (egg boiled or poached sometimes substituted), honey, 2 drachms

7 p.m.—The same as at 12 noon

Protein fat carbohydrate = 10 0.36 20

**Routine**—The patient must be confined strictly to bed during the first few stages of the treatment, as bodily and mental rest are as important as in the treatment of duodenal ulcer, for example. If possible, the patient should be in an institution and should also have a special day nurse unless the institution is very well staffed. If treated at home, he must have a day and a night nurse, and the former should be carefully selected, and, if possible, should have had previous experience of sprue.

*The first stage of the diet should be adhered to for at least ten days,*

one, back to the first stage

The patient may be allowed to get up for defæcating and washing during the fourth stage, and to sit up in a chair for part of the day during the fifth stage.

The injections of liver extract (the whole liver extracts are usually better than the more refined ones, and they must be given in generous dose

and the form of calcium lactate or basic triple phosphate in doses of 2 drachm thrice daily

Cortin appears to aid fat absorption in some cases, and should be given a trial

**Symptomatic treatment**—In the management of treatment, a full any tendency to constipat in the bazar in India, or should be given regularly in preference to liquid

effective absorption of vitamins. The atonic condition of the bowel may have led to a constipated condition in which there are large fæcoliths in the bowel that may necessitate warm oil enemata for their removal

It is probably not advisable to interfere too much with the looseness of the bowels if it occurs in the early stage before treatment has had time to take effect, but later, if the diarrhoea is troublesome or disturbs the patient, opium or bismuth should be given. A course of

sulphapyridine produces surprisingly satisfactory results in some cases of obstinate diarrhoea

water after meals

When there is gross emaciation intravenous glucose, 200 c.cm of a 25 per cent solution of glucose together with 10 units of insulin and for cramps or tetany parenteral calcium and parathyroid by mouth, should be given

chlorate mouth wash a diachm to the pint or optochin should be used or if the mouth is painful glycerine and borax, with 2 grains of cocaine to the ounce in extreme cases when the soreness is interfering with the taking of nourishment

**Convalescence**—Exercise must be graded carefully and the patient should not be allowed to return to full work for two or three months

Home leave is the ideal solution if it is during the summer but an

The question

If he has

DIARRHOEA)

ite within

t depend on

whether the food and accommodation is all right to be sent out of station

this that individual should be recommended to return to a temperate climate where for some time he may still have to consider his diet The long continuance of restricted diet is also a precipitating factor and must be guarded against If such a diet is inevitable, then extra vitamins must be given

**Prognosis**—This is dependent on the stage at which the patient comes under observation the co operation of the patient and the facilities for proper treatment If the treatment is undertaken early the prognosis should be good but it may be necessary for the patient to leave the tropics, this is particularly the case if the symptoms developed after short residence as it will indicate that the patient is particularly predisposed to the condition

At the other end of the scale if a patient is grossly emaciated with a distended abdomen has serious macrocytic anaemia and is unable to take

solid food on account of extreme soreness of the mouth, the prognosis is grave, but not hopeless if conditions for treatment are optimal

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**Definition** —Para sprue is a disease of dietary origin in which there is a watery diarrhoea of long duration, loss of weight, a sore red tongue, and later marked macrocytic anemia, it occurs in the European sojourner, the domiciled European and Eurasian, and the native in the tropics

## 

patient is kept on a low fluid diet for a long time, it is found amongst pregnant women (Napier and Edwards, 1941) It also occurs in poorer-class Europeans and Eurasians and in economically-higher classes of these two groups following long continued bowel disturbances

### 

Little is known of the morbid anatomy of this condition

4 per cent of normal persons

**Stools** —They are usually watery and light in colour, but not the bulky, frothy and pale stools of sprue, there is often some increase of fat, but the total fat is seldom above 30 per cent of the weight of dried faeces, with the normal proportion of split fat



# HILL DIARRHŒA

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Discussion.—The literature on hill diarrhœa goes back nearly a hundred years; it presents a kaleidoscopic series of pictures of the possible or probable ætiology of this condition, which all seem totally disconnected, each writer's contribution being mainly destructive of previous theories and presenting very little in the way of constructive contribution to the problem. Some of the theories that were put forward were that it was a form of scurvy—even at that time (1854) known to be due to lack of fresh fruit and vegetables; that it was a disorder of the liver due to the low tempera-

station. Nearly all hill stations are appallingly insanitary and much of the diarrhœa is due to mild *Bact. flexneri* infections acquired through water, milk or food, particularly the latter which is usually infected by flies. The the early writers and which fre- us nature of the disease. Another

of cases which does not quite fit any of these suggested ætiologies, namely

to the plains and this patient does not suffer in the same way when he returns to a cold climate in Europe. This only constitutes a very small percentage of the cases of hill diarrhœa, but the writer believes that such



demand for the raw material for additional blood formation might lead to a lower rate of wastage and again decreased bile formation. Decreased bile will lead to a condition of the bowels varies, so that the condition is different than in others.

**Symptomatology.**—This will naturally vary according to the cause. The usual experience is a watery diarrhœa, which starts very soon after the patient reaches the hill station, and is accompanied by mild constitutional symptoms, microscopical examination shows a cellular exudate but seldom any blood, suggesting a mild bacillary dysentery.

In true hill diarrhœa—if there is any such condition caused by the climatic effects only and the writer believes that there is—the stools are very similar to those of sprue, the main defect is an increase of fat which in some cases is associated with a deficiency of bile. There will be a large fluid, fatty stool.

There are arrivals at a hill station—and a certain amount of lassitude, but otherwise the subject does not feel particularly ill, and he is able to enjoy, but not to the full, his holiday, or to carry on his work, as the case may be.

**Treatment.**—The treatment of the infective type is with sodium sulphate in 2-drachm doses every four hours during the first day or two, followed by kaolin or bismuth, as in mild forms of bacillary dysentery. More severe forms may require sulphapyridine or sulphanilyl-guanidine.

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pepsin two hours later

# LEPROSY

by  
John Lowe M D

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**Introduction**—In the last two decades it has become increasingly realized that in different countries there are marked variations not only in the incidence but also in the severity of leprosy. In some countries *e.g.* parts of India and of Africa leprosy is very common but often mild. In other countries *e.g.* parts of the Philippine Islands and of South America the disease is less common but considerably more severe. In still other countries *e.g.* parts of South China, of Burma, and of South America, the disease is both common and severe.

An unbalanced and depressing view of leprosy may be the result of studying leprosy in countries where the disease is usually seen in severe forms, and particularly when such studies are largely confined to severe cases seen in leprosy institutions. Such studies appear however not infrequently to have formed the basis of accounts of leprosy in medical literature.

The description of leprosy given here is based on long experience of leprosy in the general population of India supplemented by experience gained in brief visits to other countries, and by a thorough study of the literature of the disease.

In most parts of India, the milder neural type of the disease predominates, and slight abortive cases of leprosy are common, even the cases of the severer 'lepromatous' type are frequently less severe and progressive than those seen in some other countries. It will, therefore, be found that the picture of leprosy presented here is on the whole less depressing than that frequently presented in medical literature. The disease is not described as highly infectious, nearly always progressive, and sooner or later but invariably fatal.

It is however believed that the description given here can be applied, with minor modifications, to leprosy in any country, and that probably nowhere in the world is the prognosis of leprosy so hopeless as is often suggested.

**Definitions.**—Leprosy (Synonyms—*Lepra* *Elephantiasis Graecorum*, *Lepra Arabum*) is a disease belonging to the group 'infective granulomata', is caused by *Mycobacterium lepra*, and is transmitted from man to man, mainly if not entirely, by contact.

The disease is of two main types, the *neural* type, which is mild, and the lesions are confined to certain areas of skin and/or to certain peripheral nerves and the tissues supplied by them. The *lepromatous* type is relatively severe and progressive, and the lesions are usually widespread in skin and mucous membranes, and to a less extent in the internal organs, the vital organs however show little or no affection.

The definition of these two main types of leprosy adopted at the International Leprosy Congress, 1938, was as follows—

**Neural (N) type.**—All cases of the benign form of leprosy with disturbances of polyneuritic nature (i.e. alterations of peripheral sensation trophic disturbances atrophies and paralyses and their sequelae) or macules of a non-lepromatous nature (i.e. leprides usually with localized sensory disturbances) or both. These cases give evidence of relative resistance to the infection are of relatively good prognosis as regards life although mutilation may take place and usually react positively to lepromin. Bacteriologically the skin lesions are typically but not invariably found negative by standard methods of examination though the

form of leprosy. lepromin exhibit the nerve trunks. Disturbances of all absent in the earlier stages and present in the later stages of primarily lepromatous cases, and often present in cases arising secondarily from the neural form.

Some of the points made and the terms used in these definitions are later explained more fully.

\* In our experience the nasal mucosa in true neural cases shows no bacilli.

## HISTORICAL

**Leprosy in ancient medical writings**—The earliest references to leprosy confirmed by clinical descriptions are in the ancient literature of India, the *Sushruta Samhita* (about 600 B.C.) contains definite references to, and descriptions of, leprosy but there are other probable references in still older Indian literature. The supposed references to leprosy in ancient Egyptian, Jewish, and Chinese writings of the pre-Christian era are of doubtful authenticity, no definite clinical details indicating leprosy being given, but this fact does not prove that leprosy was not prevalent in ancient times in the countries in question. In most ancient medical

generally used for leprosy, originally meant skin disease in general, the Greek word *lepra* from which name 'leprosy' is derived, originally meant a scaly disease, possibly psoriasis, and was only later applied to leprosy, as the result of mistakes in translation.

The disease was possibly mentioned by Hippocrates, and certainly mentioned and described by later Greek writers, Lucretius, Celsus in the first century B.C., and by numerous later authors in Greco-Roman times. These writers first mention leprosy as a disease rare in Italy but more common in the eastern Mediterranean. Later, the spread to Italy and to other parts of Europe is recorded by contemporary writers.

With the collapse of the Greco-Roman civilization the science of medicine was forgotten in Europe, but the Greek writings on leprosy were recovered to the Arabians, who studied the Greek writings on leprosy and wrote extensively themselves.

Europe first indirectly from the Arabian writers by the writers of the school of Salerno in Italy in the tenth century, and, later, directly through the recovery of the ancient Greek writings themselves.

During this time the terminology of leprosy became confused, and it took many centuries to clear up this confusion.

Both the Greek and the Arabian writers had used both the terms *lepra* and

The medical writings on leprosy in Europe in the Middle Ages were dominated very largely by the Greek writings, and contain little original material. Dozens of descriptions of leprosy were, however, written in the countries of Europe. Under the impression, possibly a mistaken one, that the word *lepra* (Old Testament) and the *lepra* (New Testament) were the same, the word *lepra* was applied to the medieval leprosy.

**Leprosy in modern medical writings**—The developments of scientific and medical knowledge which later followed the Renaissance were not for a long time applied to a study of leprosy, partly because by that time there was little leprosy left in Europe. It was only in the nineteenth century that the Norwegian workers Danielssen and Boeck, and later Hansen made the studies which led to the scientific work on leprosy,

especially in the last forty years. This work has established leprosy as a disease showing many points of resemblance to tuberculosis, and also some important differences.

To the modern literature of leprosy, workers of many nations have made notable contributions:

d in Norway by Danielssen and Boeck  
later by Lac and others. Other workers  
Arning, Ehlers, Marchoux, Jadassohn,  
Radcliffe-Crocker, Paldock, Tonkin.

Numerous United States workers have studied leprosy in America, Hawaii or the Philippine Islands; amongst these workers are included Dyer, Hopkins, Denny, Dean, Hollman, Macdonald, Heiser, McCoy, Aycock, McKinley, Soule, Wayson, Wade, Cole and Hesselbline.

In the Philippine Islands Filipino workers include Rodriguez, Lara, Velasco, Mansalang and Chiyuto.

In India organized leprosy research was initiated by Rogers and carried on by Muir. Later workers include Chatterji, Cochrane, Dharmendra, Henderson, Lowe and Santra.

In Japan leprosy workers have been very numerous and have included Sugai, Ota, Sato, Asami, Mitwada, Hyashi and Uchida.

In South America in recent years leprosy work has much developed and among the writers have been De Souza, Araújo, Balina, Fernandes, Fidanza, Schijman, De Souza Campos, Rotberg and Rebello.

In the French colonies have worked Delmotte, Tréoult, Montel and others; in the Dutch colonies de Jongen, Lampe and Sitansala and in the Belgian colonies D'Amor, Degotte and Radna.

In Australia workers have included Ashburton, Thompson, Cilento and Moleworth; in South Africa Mosser, Mitchell and Strachan.

In other parts of the British Empire Frazer and Rynie (Malaya), Rose (West Indies), Simon (Ceylon) and Austin (Fiji) have worked on this subject.

In China workers have included Maxwell and in Korea Wilson.

The writings of these and many other workers are largely contained or abstracted in *Leprosy Bibliography Internationale* (1900 to 1914) and the *International Journal of Leprosy* from 1933. These publications and also the other publications mentioned in the bibliography have been used in the preparation of the present chapter but it has been considered inadvisable to burden the text with hundreds of references. A select bibliography is given at the end of the chapter.

**The history of the disease**—This has already to a considerable extent been outlined in the preceding discussion. Leprosy has been common in India, and probably in Africa and China for many centuries. In classical times leprosy invaded the Mediterranean countries and later it spread over most of Europe including the British Isles. For about a thousand years it was common in these areas and then between the fourteenth and sixteenth centuries, it declined markedly although it persisted and still persists in some foci in Europe chiefly in the countries bordering the Mediterranean and to a less extent in Iceland, Scandinavia and the Baltic countries.

The decline of leprosy in medieval Europe has been attributed to segregation measures, to improved hygienic conditions and diet, to climatic changes and to the development of racial immunity. None of these

More recent still is the spread of leprosy to Australasia and the Pacific area. Here Chinese immigrants have played an important part. In Australia the disease has become endemic only in the north, chiefly in Queensland, but a few cases are found in other areas, both white and coloured people being affected.

In the Pacific, within the last century, leprosy has assumed epidemic

accelerated, by control measures.

The history of leprosy, therefore, is one of persistent endemicity in many tropical and sub-tropical countries, with periods of invasion into temperate and even cold climates, these periods however being sometimes of very long duration.

## ÆTIOLOGY

The causal organism is the genus *Mycobacterium*, and the fungi. It is rod-shaped, 2 to 4 microns in length, and is broadly slightly curved, and it frequently shows in its protoplasm dark staining granules, which may be multiple and small, and distributed evenly along the length of the organism, or may be single and large, occupying either the middle or the end of the organism. The bacillus is stained readily by the Ziehl-Neelsen technique, that is to say it is acid-fast, and it is gram-positive.

In active lesions of the neural type, the bacillus is found, but often only with great difficulty. In lesions of the lepromatous type, the bacilli are very numerous, and they show a marked tendency to occur in round masses, *globi*, which occupy large vacuolar spaces in the infected cells. It is this characteristic which enables a distinction to be made between the tubercle bacillus and the leprosy bacillus in the tissues. In other respects the two are morphologically identical.

Injected bacilli are found where, but their

generalization of the disease. It appears that, up to the present, the only animal found susceptible to the organism is man. Numerous attempts at experimental inoculation of human beings have been made, with positive

usually immune

Viability.—In the circumstances outlined above, we have very little evidence regarding the viability of the organism, and it is impossible to say

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Congenital infection does not occur - Infection *in utero* has occasion-  
ally been reported (at post-mortem examination) but it can very rarely  
be followed by the development of the disease, for children separated at  
birth from leprous parents practically always remain healthy. The general  
opinion is that transmission by air, by food and water, by biting insects

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bacillus

important in preventive work

The idea has, however, occasionally been suggested that bacilli cannot be demonstrated in them,  
Such ideas are usually based on the fac

not known as such to others. In a recent epidemiological study carried on



in villages in one part of India in 80 per cent of the new cases arising during the period of the study infectious contact could be proved

Strong support of the view afforded by a recent careful Philippine Islands in which it the family contacts of closed of leprosy in the general population with no known contact while in contacts of open cases the incidence was of course much higher

## IMMUNOLOGY

There is no doubt that the degree of natural susceptibility to leprosy in different persons varies considerably Under Epidemiology the various factors which may have an influence in this matter are discussed

There is also considerable evidence (*vide infra*) that acquired specific immunity to leprosy occurs but there is no completely specific test for such immunity There appears to be however a definite element of specificity in the lepromin test

The lepromin test was originated over thirty years ago by Mitsuda and consisted of the intra dermal injection of a minute amount of an emulsion made by grinding up lepromatous tissue rich in bacilli and previously sterilized by boiling A positive result is indicated by the development during the next few weeks of a small nodule at the site of injection A positive result is commonly seen in cases of the neural type particularly tuberculoid cases in healthy contacts particularly adults and in some healthy non contacts particularly adults A negative result is seen in cases of the lepromatous type and in healthy young children contacts or non contacts The completely negative result seen in cases of lepromatous type is a striking feature of the test and it is possibly analogous to the negative result seen in some very advanced cases of tuberculosis

Numerous later workers particularly Dharmendra have introduced improv and re shown free from by weight

Recently Fernandez has shown and others have confirmed that the late nodular reaction is preceded by an early (24/48 hours) reaction of the tuberculin type which is of the same significance as the late nodular reaction It has moreover been found that by breaking down the bacilli by physical methods defatting and grinding the early reaction can be enhanced and the late nodular reaction can be almost abolished

has been much reduced without any appreciable positive results in neural cases

There appear to be two factors contributing to a positive result in the and the other non specific and so far it has been factor Until this is done gnosis In healthy leprosy will





The incidence of leprosy in endemic areas and countries varies markedly. It is noticeable that, compared with some other chronic infective diseases, the incidence of leprosy is never very high. An incidence of more than 10 per cent of the population of an affected area is very rare and

and other parts of southern and eastern India, most of these areas being low lying, hot and humid, the incidence of leprosy is generally high, 0.5 to 3 per cent, and may be 5 per cent or more in certain areas. In individual villages the incidence

In other endemic continents and sub-continents for example, Africa and South America

ing incidence have revealed the following interesting facts regarding the type-distribution of cases. In India, in areas where the incidence is high, most of the cases, usually 70 per cent and sometimes even 90 per cent or more, are of the neural type, often of the tuberculoid variety, and many are slight and abortive. In contrast with this, it is found that in other areas, and commonly where the incidence is

in Africa, etc., they are possibly appear to predominate. In countries, including Burma, the Philippine Islands, Japan, South China and also South America, lepromatous cases appear to form a high proportion often a much higher proportion

at different ages are exposed to infection 1 per cent, while children of 50 per cent or more. These differences may not be entirely caused by the age factor. Other possible factors are mentioned elsewhere.

It is also suggested that, if leprosy is contracted early in life, it is more likely to take a serious form than if contracted later in life, but evidence on this point is not

Th a few age-groups are studied in two ways. In incidence in different the population. More a study of the age-distribution of the cases detected in surveys. Here three age-groups are considered up to 15—the early age group, 15 to 34—the middle age-group, and 34 and over—the late age-group, these age-groups being chosen because in India they are of approximately the same size, and because accurate ages may be unobtainable.

In most endemic areas, the largest number of cases, and sometimes the highest incidence, will be found in the middle age-group. This finding, however, does not indicate the age when the disease is acquired, for leprosy is a very chronic disease with a long latent period. Studies of the age of onset indicate that symptoms most commonly appear at the period a few years before and after puberty and, when the latent period is allowed for, it appears that most leprosy infections are contracted in childhood or early in adult life.

While the highest number of cases is generally found in the middle age group, marked variations are found both in the relative incidence and in the proportion of cases in the early and late age-groups. The findings in this respect may vary in different countries and in different parts of the same country, and also may show some relation to the type-distribution which has already been discussed.

In areas in which the severer lepromatous forms of the disease are common, leprosy frequently shortens life, so that the number of cases and the incidence in the late age-group is relatively low. At the same time the infectiousness of the lepromatous cases is sometimes associated with

sy in children and young people. In such of the cases is found in the earlier age-the late age-group

state of things found in areas where the mild neural type of the disease predominates. These mild forms of the disease do not appreciably shorten life, and the result is an increase in incidence with increase in age, and a high proportion of the cases in the late age-groups. Together with this the low infectivity of most of the cases is often associated with a relatively low incidence in children.

There are of course areas in which the type-distribution and age-dis-

different countries but sometimes in different parts of the same country. In some countries including many parts of India, the proportion of frank lepromatous to neural cases in the early age-group is low, and shows a relatively small rise in the later age-groups. Such findings indicate that the disease is relatively mild and often not progressive.

In other areas, however, the proportion of frank lepromatous cases in children may be higher, and in the later age groups lepromatous cases may be in the majority. Such findings indicate that, in these areas, the disease is relatively severe and progressive.

The importance of type- and age-distribution of cases is now being increasingly recognized, for crude incidence figures may give little indication of the public-health importance of leprosy in any area. A high incidence, if associated with mildness of the disease, as shown by the figures for type distribution, and a low proportion of cases in young people as shown by the figures for age-distribution, may be considerably less serious than a lower incidence of leprosy in its severer form, with the infection of numerous young people.

**Sex incidence.**—Studies of leprosy in the general population have shown that, in most parts, the incidence is higher in men than in women, and is found even in childhood. Also females tend on the whole to show milder forms of the

disease. The reasons for these differences are not clear. The possible causes are an inherent lower susceptibility of females or a less degree of exposure to infection.

**The influence of heredity. Race** — There is considerable evidence to show that the severity and the forms of leprosy vary quite markedly in different countries and it has been suggested that some races are more susceptible to leprosy than others. These suggestions have been borne out in the same place for example, in the Malay Islands, Indians and Burmans in the West Indies and Europeans and workers. No matter where the

ceptibility to leprosy of a race with the length of the period of endemicity in that race. For example the Chinese among whom leprosy has been endemic for many centuries appear relatively highly susceptible to leprosy

tropics will very rarely get leprosy but when he does he will often get it in a severe form. In the southern part of the United States particularly Louisiana the large Negro population in spite of relatively poor hygienic conditions shows a much lower incidence of leprosy than the population of European descent especially French and German. These facts indicate that the postulated acquired immunity of European races if it was ever a reality may have died out since leprosy died out in Europe. At any rate at the present time Europeans often show relatively little immunity. Our knowledge of this subject however is very incomplete but it is clear that race is of importance.

**Familial susceptibility** — From ancient times it has been realized that leprosy often runs along certain familial lines and this gave rise to the belief that leprosy was hereditary. This idea has been disproved. The possibility of susceptibility to leprosy being hereditary however has to be considered and a suggestion has frequently been made that in certain families certain persons exposed to infection develop the disease far more readily than persons of other families similarly exposed to infection and this suggestion is supported by a certain amount of evidence. Accurate

An interesting suggestion has been made that the rarity of marital

If susceptibility to leprosy were truly hereditary it should be inherited according to Mendelian law and there is also a remote possibility that 'somatic linkage' between this possibly hereditary factor and some other

easily recognizable hereditary factor might be found. As Wiener points out, this can only be done by studying three generations of affected families and, as far as is known, this has not been attempted.

The idea that leprosy is more common or more severe in persons of certain Landsteiner blood groups than in others has been suggested, but the author and others have failed to confirm this. The blood groups are of course entirely hereditary. The blood grouping of cases of leprosy of all types shows no significant difference from the blood grouping of healthy persons of the same population.

It will be seen that definite evidence regarding familial susceptibility to leprosy is scanty, but it is a matter of common experience that some persons may acquire leprosy from very slight contact for a very limited period, disease, susceptible

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the disease. High associated with a low be of more impor- in detail, however,

certain facts are revealed which are not in accordance with these ideas. For example, in the very humid eastern part of Bengal, leprosy is considerably more common than in the drier western part of Bengal. Dry central Burma is less common than the more humid southern Burma.

Climate is only one of a number of factors. The fact that leprosy used to be common in temperate and cold climates indicates that a high temperature is not necessary for transmission, but the fact that infectious cases of leprosy imported into or repatriated to European countries, although often not isolated, very rarely give rise to secondary cases, indicates that, under certain conditions, a high temperature is necessary.

In spite of the fact that leprosy is common in cold countries rarely occurs in warm countries, it is the progress of the disease, disease of warm countries, it is the common experience that persons suffering from leprosy in cold and temperate climates are often cured physically by a removal to a warmer climate.

It is a common idea that leprosy

During recent years, it has frequently been pointed out that, in Asia, the disease is more common in areas where rice is grown and forms a direct causative factor. In rice areas may be caused more by climatic and racial factors than by a diet factor.

A lack of salt has been mentioned in connection with a high incidence of leprosy, as well as the consumption of the toxic foods. The idea has been advanced that the disease is of antiquorum, of leprosy.

in many tropical areas but the evidence to support this theory is of a very similar nature to and as completely unconvincing as the evidence which Hutchinson quoted to support his fish eating theory of the causation of leprosy

Largely from analogy from other similar diseases such as tuberculosis than the consumption spread of leprosy in the individual that have been made

spread

infection is introduced



still recognizable, are often widely separated by whitish streaks of chronic inflammatory tissue. These tissues may have undergone caseation and, where the areas of caseation are large, nerve abscesses may be formed. In chronic long-standing cases of the neural type, the nerve, instead of being thickened, may be thin and atrophic, and consist of little more than fibrous tissue.

In the areas supplied by affected nerves, trophic lesions will often be found in the bones. The only enlargement of bones is in the form of tuberculoid lesions, which are marked.

of the simple variety of leprosy. In the 'simple' variety of leprosy, there is infiltration of the small round cell type, partly diffuse, partly peri-vascular and to some extent as in the tuberculoid variety. The changes are relatively simple and early leprosy.

matous changes

In lesions of the 'tuberculoid' variety, whether in the skin, the cutaneous nerve, or the nerve trunk, the characteristic histological appearance is very similar to that produced by infection of the tissues with tubercle bacilli, hence the term 'tuberculoid'.

The lesions consist essentially of small foci of epithelioid cells, often surrounded by areas of round cell infiltration, and often in the centre showing Langhan's giant cells and occasionally necrosis. (It is this necrosis which causes the nerve abscess, and the ulceration of the skin patches occasionally seen.) The small foci frequently coalesce and form large masses. In these lesions, bacilli are usually relatively few, and may be very difficult to detect in smears or sections. For some reason which is not clear, in the neural type of leprosy there is a marked tendency for these lesions to appear in the terminal nerve branches in the skin, from whence the changes spread up the subcutaneous nerves, and frequently cause marked lesions in the nerve trunks. Hence the anaesthesia and nerve involvement in the neural type of leprosy.

In the neural type of leprosy, these changes are found only in certain sites, namely, in certain areas of skin, in cutaneous nerves and nerve trunks, and sometimes in lymph nodes. There is no similar involvement of the skin as a whole, or of the mucous membranes, internal organs, etc.

**Lepromatous type.** Morbid anatomy.—The changes in the skin are described in the active phases of the disease the skin is and has a greyish white colour on section and infiltration in the subcutaneous tissues. Peripheral nerves may show thickening, usually of slight or moderate degree, over a considerable part of their course. There is frequently a slight generalized involvement of lymph nodes and lymphatic vessels. The alimentary tract is affected only at its upper end, with infiltration of the liver and spleen.

the liver and spleen caused by a chronic interstitial infiltration, and these organs may show a slightly irregular surface and a mottled appearance. Infiltration and enlargement, but the heart shows little affection, the heart is usually being normal, but the veins in

the affected tissues often show slight chronic inflammatory changes. The

lepromatous lesions are found, their character from those seen in lesions of the neural type. The epithelioid cells are few and Langhan's cells are absent. There is no marked tendency towards the involvement of nerve as compared with other tissues, most types of tissues being invaded. The characteristic cell is the histiocyte in which the protoplasm frequently undergoes fatty change with the formation of vacuoles which may be filled with fatty material and masses of acid-fast bacilli ('foamy' cell of Virchow). In this type of lesion, bacilli are demonstrated in large numbers with great ease. Such lesions are found in the skin, the nerves, the mucous membranes, the lymphatic glands, the bone marrow, and the internal organs.

## SYMPTOMATOLOGY

There is almost invariably a considerable latent period between the time when bacilli enter the body and the definite appearance of the signs of leprosy but it is only in exceptional circumstances that the time of the transmission of infection can be fixed with any accuracy. In such cases, latent periods as short as a few weeks and as long as twenty years or more have been reported. Some books describe prodromal symptoms with malaise, fever, rigors and pains in various parts of the body as commonly occurring before definite signs of leprosy appear and before diagnosis becomes possible.

In the experience of the writer and he believes, of most other leprosy workers, such prodromal symptoms are very rare. Such symptoms are not common even some time after clear signs of leprosy are evident. Such reports suggest strongly that the diagnosis of the disease has been unnecessarily delayed until the disease has become generalized and 'reaction' has occurred.

In countries such as India the onset is usually gradual and a single initial slowly spreading lesion. Some workers have suggested that the site of the lesion is at the site of the initial lesions being primary cannot be ignored. In other patients, the lesions from the start are multiple. Several patches may appear in various parts of the body, and slowly spread. In other countries, and even in India in those persons who are more highly susceptible, the onset of the disease may be much more sudden and there may be a rapid appearance of lesions in many parts of the body, sometimes with malaise, pain in the limbs, fever, etc., cases with such an onset however are relatively few.

**Types of leprosy**—Leprosy is usually a generalized or systematic infection, and the infection is rarely if ever confined entirely to one particular tissue (although in certain cases the recognizable lesions may be so confined). Clinically, however, leprosy shows itself in two main forms to which the term *neural* and *lepromatous* are now being applied. The definition of these two main types of leprosy adopted at the International Leprosy Congress, 1938, has already been given. The common clinical manifestations of these two main types are here described.

## NEURAL TYPE

The lesions seen in cases of the neural type can be divided into two varieties for which the terms *macular*\* and *anæsthetic* may be used

The macular variety (see plate XV) — There appear in the skin one or more patches usually clearly defined, round, oval, or irregular in shape, in which one or more of the following changes are found —

- (a) Loss of pigment
- (b) Diminution in cutaneous sensibility
- (c) Dryness due to impairment of sweat function, scaliness, failure of hair growth, etc

The loss of pigment is usually not complete. It may be more marked in the centre of the patch, and may be accompanied by erythema, tinged, by

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sensory changes detectable by the physician are often accompanied by sensory changes described by the patient, such as feeling of hyperæsthesia, and formication, pain and tingling when the part is struck

The thickening of cutaneous nerves supplying the macule may not be easy to detect, although sometimes it is marked, particularly in cases with marked thickening of the macules. Careful examination made with a knowledge of the distribution of cutaneous nerves will, however, not infrequently reveal nerve thickening, and this thickening may be traced from the patch up the cutaneous branches into the nerve trunks, which may also be thickened (see plate XVI, figures 1 and 2)

Thickening and erythema of the skin are often present in active macules, but they vary greatly in extent and degree. They may be very slight, and affect only the extreme margin, they may be more marked, and affect the whole outer zone of the patch, they may be very marked and in some cases they may be accompanied by scaling or by actual ulceration. Flat patches often become flat again. The thickening of patches may be very rough and uneven, and sometimes patches have a mottled appearance (see plate XV, figures 2, 3, and 4)

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PLATE XV — LEPROSY NEURAL TYPE 'MACULAR LESIONS'

- Fig 1 — Simple macule. Flat pale slightly anæsthetic patches in a child
- Fig 2 — 'Minor tuberculoid' lesion on the back. Slight irregular thickening and erythema at the spreading margin. Definite loss of sensation
- Fig 3 — Major tuberculoid lesion. Marked irregular thickening and erythema of the whole outer zone of the patch. Patch completely insensate
- Fig 4 — Major tuberculoid lesion on the back. The whole patch thick, rough red, and completely anæsthetic



Fig 1



Fig 2



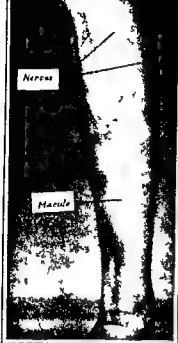


Fig 1



Fig 2



Fig 3



Fig 4



## Sub classification of macular lesions —The International Congress on

previously been of this nature

The degree of tuberculoid change in these patches may be indicated by the terms *minor tuberculoid*, *tuberculoid* and *major tuberculoid*. The tuberculoid variety of macular lesions is often associated with nerve involvement which may be great. It should be emphasized that the different patches in the same patient are usually all of the same clinical variety.

This sub classification is of considerable importance because the dif-

diameter) or very large (a foot or more in diameter). There may be only one ;  
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Bacteriological examination of these lesions usually gives negative results though sometimes a few bacilli are found and occasionally (usually during temporary phases of reaction) bacilli are fairly numerous.

The anæsthetic variety —This form of neural lesion is characterized by the occurrence of leprosy involvement of the peripheral nerve trunks. This may arise as the result of an ascending infection spreading up the

(a) Impairment of cutaneous sensibility in the area supplied by the nerve starting peripherally and extending up the affected limb

(b) Impairment of sweating and consequent dryness and scaliness of skin in affected parts

(c) Paresis or paralysis with wasting of muscles supplied by affected nerves

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infection of trophic

lesions

Perhaps the commonest nerves to be affected are the ulnar nerve, the peroneal nerve and the posterior tibial nerve.

# PLATE XVI—LEPROSY NEURAL TYPE NERVE INVOLVEMENT

Fig 1—Thickening of cutaneous nerves supplying a patch on the forearm

Fig 2—Thick branches of cervical plexus supplying patch around the ear

Fig 3—Paralysis of 5th and 7th nerves. Anæsthesia of cornea and inability to close the eyes

Fig 4—Trophic ulcers of foot caused by tibial nerve involvement

Fig 5—Nerve abscesses of ulnar nerve exposed at operation. Two abscesses and markedly thick nerve between are seen

The affected nerve is usually thick, sometimes very thick, particularly the ulnar and peroneal nerves. Sometimes the involvement of nerves causes nerve abscess (*v 1*, and see plate XVI, figure 5)

The lesion of the ulnar nerve is most marked above the elbow, this lesion produces anæsthesia of the little and ring fingers, and on the ulnar side of hand and forearm, and later paralysis of small muscles of the hand, with the development of the typical deformed 'claw hand' of ulnar paralysis. The peroneal nerve is often affected where it passes round the neck of the fibula. The result is anæsthesia of the dorsum of the foot and of the outer side of leg, and paresis of the peroneal muscles with the development of 'drop foot'. The posterior tibial nerve is commonly affected on the inner and posterior aspect of the ankle, and the result is anæsthesia and keratosis of the sole of the foot, and trophic ulcers (see plate XVI, figure 4)

Other nerves sometimes affected are the radial nerve, the median nerve, the fifth and seventh cranial nerves and the great auricular nerve. The

orbital and facial muscles, ectropion, and lagophthalmos, with great liability to irritation of the eye by unfelt foreign bodies, conjunctivitis, corneal ulcer, etc (see plate XVI, figure 3)

In marked cases of the neural type of the anæsthetic variety, there may be anæsthesia of all the limbs and of most of the trunk and face, and paralysis, trophic lesions, and deformities in the arms, legs, and face

or tuberculoid, and the nature, significance and the course of the nerve trunk involvement are likely to be the same as those of these patches

permanent disability caused. The less marked forms of nerve thickening are more likely to be of 'minor tuberculoid' or 'simple' nature, with less immediate damage but a greater tendency to chronicity and extension, and even to lepromatous development

The neural type in general.—The chief clinical manifestations of the neural type of leprosy have been outlined. Both types of lesion, macular and anæsthetic, may be present in the same patient. For practical purposes, in cases of the neural type, we may regard the infection as being confined to the macules in the skin and to the affected cutaneous nerves and nerve

PLATE XVII—LEPROSY	NEURAL TYPE	TUBERCULOID REACTION AND SPONTANEOUS SUBSIDENCE
		Iteration of tuberculoid lesion on face
		Discharge
		Complete subsidence no bacilli found
		Very slight temporary lesions appeared

elsewhere

Fig 3—Marked general tuberculoid reaction

Fig 4—Same patient about a year later. Subsidence was complete and permanent (Eighteen years' observation)



Fig 1



Fig 2

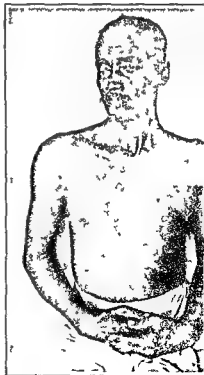




PLATE XVIII



Fig 1



Fig 2



Fig 3



Fig 4

trunks There is as a rule no constitutional disturbance except in cases with secondary infection or with reaction (*vide infra*)

Of all the symptoms described above there are only two which are diagnostic of leprosy namely definite thickening of nerves and impairment of cutaneous sensation (see Diagnosis)

There remain to be discussed certain matters common to cases of the neural type in general

**Nerve abscess**—One curious feature of leprosy of the neural type seen in India and particularly in Bengal is the not infrequent occurrence of oval or circular swellings on leprosy nerves. The swellings may occur in cutaneous nerves when they are usually small (the size of a pea) or in nerve trunks when they may be much larger. The swellings are cold abscesses which may burst into the surrounding tissue and may discharge

**T**

sometimes in large numbers or previously undetected lesions may be rendered easily detectable. At the beginning of the reactionary phase there is often an increase in the number of bacilli detectable in smears taken from the lesions and previously negative lesions may become positive.

The condition of reaction in neural cases is always a temporary one and it subsides spontaneously sometimes in a few weeks or months but the reaction may cause severe damage to the nerves with permanent disability and deformity. Reaction of the variety described in cases of the neural type although its appearance may be alarming is often not a bad prognostic sign since it is frequently followed by long periods of inactivity of the disease and it may be followed by permanent arrest of the disease. In a few cases however reaction may recur even several times and at short intervals.

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In some cases the number and the size of the lesions may show little or no increase over long periods while in other cases the size and number of the

PLATE XVIII.—LEPROSY. LEPTOMATOUS TYPE.

F = 1 - S      1    2    3    4    5    6    7    8    9    10    11    12    13    14    15    16    17    18    19    20    21    22    23    24    25    26    27    28    29    30    31    32    33    34    35    36    37    38    39    40    41    42    43    44    45    46    47    48    49    50    51    52    53    54    55    56    57    58    59    60    61    62    63    64    65    66    67    68    69    70    71    72    73    74    75    76    77    78    79    80    81    82    83    84    85    86    87    88    89    90    91    92    93    94    95    96    97    98    99    100

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patches may increase steadily, and the number of nerves involved and the degree of involvement may also increase. This increase in the size and the number of lesions may be extremely gradual, or, in cases with reaction it may be sudden and marked. In some cases, the extent and degree of skin involvement may show little or no increase while the extent and degree of involvement of the nerves and nerve trunks supplying the affected areas may increase markedly, with resulting deformities trophic lesions etc.

There are some cases of the neural type which tend to develop into cases of the lepromatous type, but recent studies have shown that this change from neural to lepromatous type is relatively rare, and is largely confined to neural cases of the 'simple' variety.

The course of the disease in cases of the neural type varies markedly with the sub type.

(i) *The course in neural cases of 'simple' sub type*—Such cases do not often remain indefinitely of this sub type a few lesions of this type may subside spontaneously. Some become lepromatous and follow a corresponding course as described later. Most of the others become tuberculoid usually minor tuberculoid and follow a corresponding course.

(ii) *The course in neural cases of minor tuberculoid sub type*—Minor tuberculoid cases are often characterized by extreme chronicity. There are some cases in which lesions remain localized and subside within a relatively short time but in many cases the slight indolent activity goes on for years with extension of the lesions of the margin and healing at the centre with from time to time the development of new lesions and also a tendency for increasing involvement of

Minor tuberculoid cases may remain mildly active for many years sometimes up to thirty years or more. In such cases apparent arrest even of long standing may be followed by renewed activity.

(iii) *The course of tuberculoid and major tuberculoid cases*—In such cases the skin lesions are clinically more marked and the degree of nerve involvement is also greater as also is the tendency to tuberculoid reaction with positive bacteriological findings but nevertheless the periods of activity of the lesions are often very much shorter and may be limited to a few months or a year or two while the tendency to extreme chronicity is much less marked.

In some cases for a short time the disease will permanently subside with numerous bacilli in the lesions, but the more marked the degree of tuberculoid activity the greater is this tendency to subsidence.

Subsidence of marked tuberculoid activity is occasionally followed by minor tuberculoid activity of long duration or after a considerable interval by short periods of recurrence of major tuberculoid activity. This recurrence however is usually not repeated many times, and the disease commonly becomes quiescent and arrested. These phases of tuberculoid activity however may cause severe damage to nerves with permanent deformity.

(iv) *The signs of subsidence in neural cases*—The patches instead of being inflamed become thinned and atrophic and signs of fibrosis in the

when reaction becomes marked in affected nerves and fibrotic. As the disease increases must not

## LEPROMATOUS TYPE

— the definition of the two main types of leprosy is seen in cases of the severer form in which there is little or no resistance to the spreading in the tissues of the body

with little or no tissue reaction. The lesions are more diffuse in nature and more widespread throughout the body than in the neural type of leprosy, for the skin, nerves, mucous membranes, lymphatic glands and internal organs frequently show invasion. Clinically, however, the chief lesions are

- 1 Slight diffuse thickening sometimes with erythema the skin having a shiny appearance and giving a soft 'velvety' feeling on palpation
- 2 Macules or circumscribed areas of skin with pigmentary change, differing from the macules of the neural type by having a smoother surface and an indefinite margin by showing no sensory change or thickening of the cutaneous nerves and by the fact that many bacilli are found on bacteriological examination
- 3 Nodule formation in the skin or subcutaneous tissue the nodules varying markedly in size and sometimes being so small as to resemble papules
- 4 Ulcers caused by breaking down of nodules

the dorsal aspect of the

hands

One of the manifestations of leprous infiltration of the skin is the loss of hair, which may be seen all over the body but is most commonly seen on

the

anæsthesia of the limbs caused by leprous involvement of the peripheral nerve trunks much less than

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thing

In the lepromatous type of leprosy, the mucous membranes are very frequently affected, the mucous membrane of the nose pharynx and larynx being infiltrated, and sometimes showing nodulation and ulceration. Such lesions in the nose may cause destruction of the nasal septum and falling in of the nose, and in the larynx may cause hoarseness and dyspnoea. Symptoms of leprous infiltration are also frequently seen in the eye (see plate XVIII, figure 4), in the form of chronic leprous irido-cyclitis and leprous infiltration of the cornea. Leprous invasion of the testes is also

**Reaction in lepromatous cases**—Reaction in the neural cases has already been discussed. A condition somewhat similar is also seen in cases of the lepromatous type, but in such cases the allergic nature of the reaction is much less clear, the clinical manifestations of reaction are often very different, and the prognostic significance of the reaction is also different.

In lepromatous cases, the manifestations of the reaction often include thickening, erythema, and sometimes ulceration of the infiltrations and nodulations in the skin and mucous membranes, the appearance of new nodules and infiltrations, sometimes very numerous and extensive, in the skin and subcutaneous tissues, and increase in the symptoms caused by leprosy involvement of the mucous membranes, particularly of the nose and of the larynx. The reaction is usually accompanied by dyspnea caused by subacute leprosy irido-cyclitis. These manifestations are usually accompanied by constitutional disturbance, fever, rigors, prostration, etc.

Reaction in lepromatous cases may be very severe, and not infrequently lasts for a considerable time, weeks, or months, and when it finally does subside, the patient's condition is often worse than it was before the reaction. Also the reaction is apt to recur periodically, with a progressive deterioration in the patient's condition. Such reaction, however, even if very severe, rarely causes death, though death from intercurrent disease during or after the reaction is not uncommon. The importance of recog-

become more marked and more widespread, and, finally, generalized. This process may be relatively rapid, taking only a few months, or it may be much slower and take several years. The process of generalization may be accompanied by the occurrence of reactions, and these reactions may occur repeatedly. On of the patient may rapidly deteriorate. In such cases, death from intercurrent disease and weakness is not uncommon, and the whole course of the disease may be only a few years. Even in such cases, however, if the patient can be tided over the period, the disease may be marked by a

begins in the disease or more, deformed. Thus two acute and rapid two extremes serious and may shorten life considerably, but subsidence with a greater or less degree of deformity and disability is not uncommon, and the prognosis of lepromatous cases, though grave, is not so hopeless as is sometimes stated.

ty years led and

in the nerves, and the atrophy of nerves is frequently accompanied by actual increase in the trophic changes, which should not be taken as indicating activity of the disease itself

### CASES OF DOUBTFUL CLASSIFICATION

of both

There may, for example, be infiltrated patches with anæsthesia and some nerve involvement, but the patches may be smooth, have an indefinite margin and show numerous bacilli in smears. Less commonly some of the lesions may be localized and appear to be neural, while other lesions may be

months the case may become more typical either neural or lepromatous, of cases in which clinical and other  
findings and prognosis  
are, and accurate classification and

### THE DISEASE IN GENERAL

The relation between the two main types — The idea that the neural

may may state to serious infection. Those persons in whom there is some degree of immunity usually show the neural form while those in whom there is little or no immunity show a much greater tendency to develop the lepromatous form

It is true that there are some cases of leprosy which are not characteristic of either of these two main types, and which show some features of both, but these cases are, as a rule, not numerous. It is also true that there are

some cases of leprosy of the neural type which later develop into cases of lepromatous type, but it is believed that these are not numerous and that they mostly belong to the sub-variety of the neural type which has been called 'simple'. The classification of cases of leprosy is not merely of academic interest, since it has important bearings on prognosis and treatment, and also on preventive work, since the lepromatous cases are the infectious cases.

TABLE XIII

Findings	NEURO-MACULAR			Lepromatous
	Simple	Tuberculoid	Tuberculoid major	
Clinical	Patches flat and smooth. Nerve thickening, slight anaesthesia, sometimes not marked.	Margins of patch show thickening, roughness often papillation. Anaesthesia definite. Nerves often moderately thick.	Thickening of patch marked and not confined to margin. Anaesthesia marked. Nerve thickening often marked.	Skin lesions smooth ill-defined, usually infiltrated, may be nodular. Mucous membranes etc., affected. Anaesthesia often found in limbs but not in skin lesions.
Bacteriological	Usually negative	Rarely positive	Usually negative, may be positive in 'reaction'	Always positive
Lepromin test	Negative or weak positive	Rarely negative, usually weak or moderately positive	Practically always positive, usually moderate or strong positive	Nearly always negative
Histopathology	Cellular infiltration not 'tuberculoid'		"	Foamy cell leproma. No tuberculoid structure.
Prognosis and course	Doubtful. May become lepromatous, may become tuberculoid or may subside.	Rarely becomes lepromatous, subsidence fairly common.	very rarely becomes lepromatous.	" more often late after long period of activity. Relapse common.

**Reaction**—There are certain points which have already been mentioned but of which further discussion is advisable. The first is the occurrence, in both of the main types of leprosy, of the acute or sub acute condition which has been called 'reaction'. The failure to recognize this

condition and the fact that it usually subsides sometimes in a relatively short time even without any special treatment has been a frequent cause

a trophic nature caused frequently by trauma in tissues the vitality of which has been lowered by the destruction of the nerves and including

deep (see plate XVIII figure 4)

## DIAGNOSIS

say that even if a case appears exactly like one of leprosy unless one of these three signs is definitely present the diagnosis of leprosy should not be made

partial and not complete and may be very definite in some lesions and only very slight in other lesions. The most useful way to test for loss of sensation is to test the sensation of light touch. The patient's eyes are shut or bandaged the skin is touched with a piece of paper or a feather and the patient is asked to indicate with a finger the place touched. Failure to respond indicates impairment. Sometimes particularly in patches on the face touch sensation is retained



while the sensations of pain and of heat and cold are lost. The sensation of pain may be tested by means of pin pricks in the suspected area and in normal skin the patient being asked to say which he feels most. In doubtful cases the heat and cold sensation may be tested.

Patience and care are necessary in testing sensation and allowance must sometimes be made for the patient's mental condition which may be dull. It should also be remembered that the skin sensation is normally dull in certain parts of the body for example over the elbows and in areas of hard thick skin.

**The detection of nerve thickening**—Here a word of warning is necessary. A nerve is not thick merely because it can be felt. Many normal nerves (e.g. the ulnar, posterior tibial, peroneal and sometimes the great auricular) are palpable and give pain on pressure. A nerve should only be stated to be thick when it is definitely more thick than the same nerve on the other side of the body or, if both sides are affected, thicker than the same nerve in a person of similar build. Examination for thickened nerves should include palpation of the ulnar above the elbow, the great auricular, the peroneal, and superficial peroneal nerves, and also palpation of the subcutaneous tissue around and proximal to macules, for thickened cutaneous nerves.

**The demonstration of acid fast bacilli**—As has been stated above this is not often necessary for diagnosis but more often for judging whether a patient is infectious or not.

**Sites of examination**—There is a common idea that the best way to demonstrate bacilli is not in the skin but in the nasal mucous membrane. This is not true. Nasal examination is highly infectious or not instead of examination of the skin.

Bacilli are rarely found in anæsthetic areas or in macules of the neural type though there may be a few found in the erythematous margins of such macules. Bacilli are found in the lesions which have been described above as lepromatous or as areas of slight diffuse infiltration thickening nodule formation etc. In cases of the latter type bacilli are frequently found in the skin of the lobe of the ear in clearly visible lesions.

The most generally useful method of examining the skin is to take up a fold of the suspected skin between the thumb and forefinger of the left hand maintaining pressure to prevent bleeding and with a sharp scalpel held in the right hand make a slit vertically downwards into the corium. Still maintaining the finger pressure with the point of the scalpel scrape the bottom and sides of the slit collecting material on the point of the scalpel. Tissue cells not blood are required. If there is excess of bleeding wipe away the blood before scraping. Make a smear of the scraping on a slide fix by heat stain and examine.

In nasal examination inspect the nasal septum for lesions take a suitable instrument and scrape away cells not blood or mucus from the lesion if visible or from the septum near the anterior end of the inferior turbinate bone make a smear on a slide fix and stain.

It is most important that the slides and instruments used in making bacteriological examinations should be clean and free from acid fast bacilli. This means that old slides should be used only after very thorough cleansing and that instruments must be very thoroughly cleaned and sterilized between each examination.

**Staining and examination of smears**—The method of staining used is that of Ziehl-Neelsen which is described in many textbooks. The most important thing is that the stain shall be properly made the basic fuchsin being ground in a

necessary amount of acid or alcohol so far as possible. For the best results that other things besides the fragments of horny acid fast bacilli. The bacilli be no doubt about the presence is doubt it is not a often very numerous. If

only one or two bacilli are found in a whole smear, it is advisable to repeat the examination in order to verify the finding.

**Cases with no cardinal signs**—It has been stated that, if none of the three cardinal signs is found, a diagnosis is very rarely justifiable. The most important exception is met in cases of leprosy in children. In young children who have been in close contact with an infectious case, one often finds on the face, body, buttocks or limbs, depigmented patches in which there are no sensory changes, no bacilli, and no thickening of nerves. In such cases of leprosy with the cases of skin in children.

A more degree of leprosy is often of very  
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antous type,  
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ry and care-

ful clinical examination and, in some cases, bacteriological examination are needed.

## DIFFERENTIAL DIAGNOSIS

There are a number of diseases which may be mistaken for leprosy

skin which may resemble  
vs Secondary and tertiary  
tions of the skin (dermal  
as, lichen planus, erythema  
Confusion may also occur  
inflammatory conditions of the

skin such as erysipelas and cellulitis. Primary syphilide may closely resemble a macule of the neural type of leprosy. Dermal leishmaniasis (a post-kala-azar condition found commonly in Bengal, Bihar, Assam and Madras) often produces depigmented patches, infiltrations and nodules, which very closely resemble those of leprosy. Psoriasis with marked scaling of the lesions may produce an apparent but not real loss of skin sensation. Leucoderma produces marked depigmentation with no loss of sensation. The absence of the three cardinal signs of leprosy mentioned above distinguishes all these conditions from leprosy.

**Diseases causing loss of cutaneous sensibility**—Many diseases of the central nervous system or of the peripheral nerves may cause some loss of skin sensation. Neuritis may be caused by toxins or by vitamin deficiency. Bernhardt's disease (neuritis of the lateral femoral cutaneous nerve), leucoderma, traumatic, some loss of sensation produced by interference with the blood supply in conditions such as Raynaud's disease and obliterative endarteritis.

Most of these conditions are rare, some of them very rare. In countries in which leprosy is common, a case of leprosy is frequently wrongly

the hands and feet, sometimes seen in Raynaud's disease and obliterative endarteritis, the deformities of tertiary yaws, deformities produced by trauma to nerves, involvement of nerves in callus formation after fractures, etc

**Multiple infections**—One point should be mentioned in conclusion Not infrequently the skin lesions of the leprosy are associated with other infections of the skin and leprosy and dermal leishmaniasis

## PROGNOSIS

The course of leprosy in its various clinical forms has already been discussed, and it has been seen how greatly this course varies. The statement sometimes made that leprosy is always or almost always progressive and sooner or later fatal is therefore seen to be extremely misleading, especially in view of the fact that in most countries where leprosy is common, the neural cases form at least 50 per cent of the cases seen, while in some highly endemic countries such as India and Africa, the proportion of neural cases may vary between 70 and 90 per cent or more, and a high proportion of these is commonly of the tuberculoid sub type

It appears desirable to outline what is meant by a good or a bad prognosis in a disease such as leprosy. Leprosy does not affect the vital organs and, in the absence of secondary infection, rarely causes death. Therefore the prognosis is concerned largely with the likely duration and

marked disability and deformity. A good prognosis in leprosy is one in which the disease may remain stationary for a long time, and will probably for many years, that during this time there is a possibility, or in highly susceptible persons a probability, of death from weakness or other disease, and that if and when the disease does finally subside, marked disability and deformity

Factors to be considered are the type and sub-type of the disease and the race of the person affected. These two factors are often inter-related since in certain races the lepromatous type is predominant, while in other races the neural type predominates.

The prognosis is, on the whole, good, but the extent of the lesions has a bearing on prognosis. In its more marked forms, the prognosis is usually excellent, whereas the presence of the kind of lesion which has been called 'simple' indicates an uncertain prognosis, since in such cases the disease not infrequently develops later into the lepromatous form.

In the lepromatous type of leprosy the prognosis is definitely poor. As already stated the race of the affected person markedly influences the prognosis. Many people of Indian and African races show leprosy in a mild and non-progressive form. In Europeans, and in persons of mixed European and other descent the disease is much more often severe and

The lepromin test, if positive, is a definite indication of a relatively good prognosis

Another factor possibly influencing prognosis is the age at which the disease appears, since children and young people often show relatively little resistance to leprosy, but even in children the definitely tuberculoid lesions have a good prognosis

The general physical condition of the affected patients and the presence or absence of intercurrent disease have frequently been quoted as having an important bearing on prognosis, but it is believed that their importance can easily be exaggerated

## TREATMENT

**Introduction**—From ancient times until recently, leprosy has been regarded as a disease for which treatment was of very limited value

but in recent and more recent years, and more recently, is it is now generally accepted that other forms of treatment

on the value of treatment have reported strikingly beneficial results from various forms of treatment, some of these reports

provided that patients suitable for treatment are selected, treatment is of definite benefit. It cannot be readily acquired

below  
diseases  
are

leprosy of the neural type, with deformities, ulceration etc, obtain little or no benefit from treatment. The severe or advanced cases of lepromatous type are frequently difficult or impossible to treat, because of frequent

The elimination of  
aria, and anæsthesia,  
regular hours, sufficient  
treatment

The term 'special'  
believed that  
that quinine  
or kala-azar or  
at forms of

**Historical**—The use of the chaulmoogra group of oils in the treatment of leprosy apparently originated in India at least 2,500 years ago for it is described

in the *Sushruta Samhita* of about that period. It has recently been pointed out that these writings are not so old as they are generally supposed to be.

many centuries ago

In the nineteenth century, European physicians in India found this oil being used by practitioners of Indian medicine, and began to take an interest in it. The oil was administered by the mouth and byunction and various workers in India and other countries tried this form of treatment some reporting some benefit, and others little or none. From 1879 onwards various chemists studied the chaulmoogra oils, isolated their fatty acids and prepared their salts and these

The ethyl esters of 1907

394 in Egypt where ted various forms of ids. The use of these

The excellent results

of the treatment was first made known particularly in Hawaii and in India encouraged treatment in most countries of the world, widely recognised it is now the standard

is in common use are hydnocarpus oil (*elmantica* etc) with 4 per cent creosote, it seems as if these

reduced by warming the oil to body must be obtained from a reliable source

**Dosage**—For recommended Be 5 or 6 c cm given

larger doses in certain suitable cases and doses of 40 c cm is given in a local reaction or pain, the doses on occurs, then only

ably given cutaneous

injections

Intra-muscular injections should be given deep into the upper part of the gluteus maximus muscle. Thorough massage of the part after injection assists rapid absorption. Subcutaneous injections are best given into the loose subcutaneous tissues of the fleshy parts of the limbs. By nearly with- up to 3 or

ions them-

a needle and about

should supervise in a second time until a month has elapsed

If all the lesions have recently been intra-dermally injected, the other two methods should be used. Usually not more than two or three cubic centimetres are given by intra-dermal injection at one time, the remainder (if any) of the dose ordered being given by other methods

The intra-dermal method is suitable for injections into the macules of the neural type and into the lesions of the lepromatous type. Good results have also been reported with injections given near and around the affected nerve trunks and into the skin and subcutaneous tissue in their distribution.

*Duration of treatment and assessing results.*—The duration of treatment varies. In slight cases of leprosy, treatment may be prolonged and prolonged. There

to relapse may at once be detected and treatment resumed.

In assessing results of treatment, accurate records of clinical and anatomical changes, if lesions disappear, the anaesthesia may become less extensive, and the bacilli, if

*Other forms of special treatment.*—As already stated, hundreds of remedies have at one time or another been used and advocated in the treatment of leprosy and every year sees additions to this number. The common sequence of events is as follows: Some worker tries a new remedy

have been used

Numerous workers have used injections of preparations of heavy metals, particularly the disease in general and also in such as eye affections but other

*Potassium iodide.*—A gradual increase from small to large doses has been used by various workers during the last sixty years.

other

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resolu

this matter reads as follows:—

'With regard to treatment with potassium iodide the use of this drug is frequently followed by disastrous results. It is therefore to be discouraged for the purposes of diagnosis, treatment, or as a test of recovery unless in very skilled and experienced hands.'

Various workers have used vaccines consisting of supposed cultures of lepra bacilli, or else sera produced by 'immunizing' animals with these vaccines, or with material obtained from leprosy patients. Examples of these preparations are Rost's 'leprolin' and Reinstein's serum. The results of such treatment are not clear --

Ever since their use in the treatment of the leprosy lesions and intravenous injections, and lesions may break down, ulcerate and then heal after large doses, but permanent improvement is usually not seen.

Various workers have reported beneficial results from the administration of preparations containing large amounts of one or more of the different vitamins. Reports of this form of treatment are very contradictory, and their value has not been proved.

One of the latest new treatments for leprosy has been the injection of diphtheria-formol-toxoid. The strikingly beneficial results originally reported have been confirmed by no one, and some workers find the treatment definitely harmful.

The induction of a high temperature either in the lesions themselves or in the patient's body as a whole has been used by various workers, and various methods of heat therapy have been employed, but the results are not striking or consistent.

**Local treatment of lesions** — In addition to the local treatment discussed later under 'Management of complications', various forms of local treatment of the lesions themselves may be used.

All workers are agreed on the value of local irritation to lesions of all types and some of the benefit produced by injection of hydnocarpus preparations may be caused by this local irritation. Various other forms of irritant have been used, such as carbon dioxide snow, but a very useful and more widely practicable measure is the application to the lesions of trichloroacetic acid. Solutions of the crystals in water of varying strengths from 1 in 1 to 1 in 4 (by weight) are used. The stronger solutions are used for touching nodules and other small but prominent lesions, the weaker solutions are used for application to larger areas of skin, infiltrations, patches, etc. The solution is applied with a small cotton-wool swab held in forceps, and the application should be followed by whitening of the skin and desquamation, but not by ulceration. A little experience is necessary in judging how much solution to apply and in what strength, and care is needed to avoid burning the skin, with the production of scars and sometimes keloids.

Another form of local treatment is the surgical removal of suitable lesions suitably situated. If the only lesion of leprosy is a single small patch, surgical excision may be practised, and is usually not followed by recurrence if the original lesion is of the tuberculoid sub-type. Sometimes more than one such patch may be excised.

allowance must be made for contraction produced by fibrosis when the incision heals

times a day with a bland fluid such as normal saline or with mild antiseptics and local applications of mild caustics or stronger antiseptics can then be made to the actual ulcers present in the nasal septum. In this way such ulcers will frequently be made to heal the discharge of the lepra bacilli from the nasal mucous membrane can be much diminished or prevented and the patient thus rendered much less infectious.

### MANAGEMENT OF COMPLICATIONS

**Reaction** —In the milder forms of reaction particularly the tuberculoid reaction seen in neural cases hospitalization may not be needed and the reaction will subside in time without any treatment beyond the cessation of the administration of hydnocarpus preparations or any other medicament which may have precipitated the reaction. Concomitant diseases present such as malaria should be treated.

In the more severe forms of reaction particularly in lepromatous cases hospitalization is necessary for proper treatment.

The patient should be kept in bed properly nursed and given suitable general treatment diet aperients etc. Various forms of medicinal treatment of reaction have been recommended such as the injection of small doses of antimony in the forms of potassium antimony tartrate given intravenously or of large amounts of forms of treatment affections severe ne as described later.

In time the fever and the other symptoms will subside and hydnocarpus treatment when resumed must be undertaken with great caution as to dosage.

**Trophic lesions** —By care it is frequently possible to minimize if not prevent the development of trophic lesions in cases of leprosy. The lesions are the result of the damage to nerves chiefly those supplying the feet and hands. Careful examination of patients may reveal marked infiltration of the ulnar or median nerves of the peroneal or tibial nerves and suitable treatment for this neuritis (*vide infra*) may minimize the nerve damage and the risk of trophic lesions.

extension of the fingers may also be of value.

If the nerves supplying the hands and feet are seriously affected steps should be taken from the hands allowed. Similarly specially made if necessary or adapted to prevent pressure on points where trophic ulcers are likely to develop such as the head of the first metatarsal or the os calcis.



The trophic ulcers of the foot are of two types, firstly the simple trophic ulcer of the sole without necrosis of bone, secondly, the trophic ulcer with necrosis of the underlying bone. In practice it is found that most trophic ulcers are of the second type.

In the absence of necrosis of the bone, the ulcer will usually heal if the patient is kept off his feet and suitable local applications are used. It is most important to prevent pressure of injury to the feet, by keeping the patient in bed or allowing him to walk only with the use of crutches, until the ulcer has finally healed. The ulcer should be kept dry and clean, and all thickened dead skin around it should be kept pared off, and the ulcer encouraged to heal from the bottom. Many different local applica-

to be of outstanding value  
be used for cleaning septic  
ulcers, but prolonged soaking in antiseptics is to be avoided. Antiseptic or bacteriostatic powders such as sulphanilamide may be used, and the ulcer may be sealed with elastoplast or plaster of paris, and the dressing changed at long intervals.

If bone necrosis is present the ulcer may heal temporarily, but not permanently unless the bone is removed or else discharges itself through the ulcer. The bone necrosis can usually be detected by the use of a probe

#### examination

The dead bone should be removed by operation, which should be carefully performed to avoid all damage to surrounding healthy tissue. Local anaesthesia is induced by infiltrations round all the nerves at the ankle. Incisions should always be made on the side or dorsum of the foot and not on the sole. In order to minimize deformity, only dead tissue should be removed. Since some secondary infection is usually present, it is inadvisable to close the incision by sutures.

Secondary infection of trophic lesions, often of a virulent nature, is not uncommonly seen, and, in the absence of proper surgical treatment is one of the commonest causes of death in cases of leprosy. It commonly leads to a perforating ulcer, but also without as the result of blood-borne infection.

In the past, early and radical surgical treatment of these acute septic conditions has been practiced in the form of amputation of digits, hand, foot, or limb, and has given excellent results, without such operations patients frequently die. Although nothing has yet been published it appears that ity for surgical treat-

such operations as  
ing results

preventive measures  
ice

type of leprosy, slight  
attract little attention  
n some patients, how-  
ye affections are very  
or sub-acute leprosy  
The patient should

be kept in a darkened room or wear an eye shade the pupil should be

etc

**Severe neuritis**—This may be seen either during a reaction or apart from it and is most common in the ulnar nerve. Palliative treatment includes such procedures as the injection of cobra venom to relieve the pain, local application of heat etc. in the form of hot compresses or of diathermy. Subsidence is frequently seen following the operation for removal of the nerve sheath around the affected part of the nerve which is frequently a limited portion of the ulnar nerve above the elbow. Such operations may also minimize subsequent deformity.

**Respiratory obstruction**—Obstruction of the larynx may be caused either by the presence of marked lepromatous lesions, especially during the phase of reaction in which case it is acute or sub acute or by the fibrosis which follows the healing of such lesions in which case it comes on very gradually. In either case tracheotomy is sometimes needed for the relief of this condition which may otherwise cause death. When the reaction has subsided it may be possible to remove the tracheotomy tube but the advisability of removal is doubtful for subsequent reactions may necessitate replacement. In cases caused by fibrosis the tube has to be kept in permanently.

## THE CONTROL OF LEPROSY

tion of careful and thorough treatment of cases of leprosy no control measures are likely to be effective for the co operation of those suffering from leprosy will not be secured nor the sympathy and support of the public

The trophic ulcers of the foot are of two types, firstly the simple trophic ulcer of the sole without necrosis of bone, secondly, the trophic ulcer with necrosis of the underlying bone. In practice it is found that most trophic ulcers are of the second type.

In the absence of necrosis of the bone, the ulcer will usually heal if the patient is kept off his feet and suitable local applications are used. It is most important to prevent pressure of injury to the feet, by keeping the patient in bed or allowing him to walk only with the use of crutches, until the ulcer has finally healed. The ulcer should be kept dry and clean, and all thickened dead skin around it should be kept pared off, and different local applications of outstanding value—chlorine antiseptics,

ulcers but  
bacteriostat

may be sealed with elastoplast or plaster of paris, and the dressing changed at long intervals.

If bone necrosis is present the ulcer may heal temporarily, but not permanently unless the bone is removed or else discharges itself through the ulcer. The bone necrosis can usually be detected by the use of a probe.

examination

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Incisions are  
on the sole  
removed

to close the incision by sutures

Secondary infection of trophic lesions often of a virulent nature, is not uncommonly seen, and, in the absence of proper surgical treatment, is one of the commonest causes of death in cases of leprosy. It commonly leads to acute cellulitis, necrosis or gangrene of the affected part. The virulent secondary blood-borne infection settling in

In the conditions has been practised in the form of amputation of digits, hand, of these acute septic such operations patients established, it appears that markedly influenced the necessity for surgical treatment by such operations as pointing results the preventive measures

already outlined should be adopted to prevent

Leprous eye affections.—In the lepromatous type of leprosy, slight eye affections may attract little attention.

In some patients, however, eye affections are very severe or sub-acute leprosy. The patient should

be kept in a darkened room or wear an eye shade the pupil should be kept constantly and fully dilated with atropine and hot boric fomentations

etc

**Severe neuritis**—This may be seen either during a reaction or apart from it and is most common in the ulnar nerve. Palliative treatment includes such procedures as the injection of cobra venom to relieve the pain local application of heat etc in the form of hot compresses or of diathermy. Subsidence is frequently seen following the operation for removal of the nerve sheath around the affected part of the nerve which is frequently a limited portion of the ulnar nerve above the elbow. Such operations may also minimize subsequent deformity.

**Respiratory obstruction**—Obstruction of the larynx may be caused either by the presence of marked lepromatous lesions especially during the phase of reaction in which case it is acute or sub acute or by the fibrosis which follows the healing of a laryngeal lesion.

but the advisability of removal is doubtful for subsequent reactions may necessitate replacement. In cases caused by fibrosis the tube has to be kept in permanently.

## THE CONTROL OF LEPROSY

The control of leprosy should be based on knowledge of the epidemiology of the disease which has already been outlined.

countries such  
as control of  
the 19th century  
of valuable  
information in various  
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(a) Leprosy surveys—In addition to the general preliminary survey  
 may be needed in the areas in which the

of leprosy in the area covered by the plan if necessary by properly

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 support

(d) Provision for home isolation of infectious cases—The main point

lated patient  
 outside the  
 not involve  
 e isolation if  
 the isolation  
 nt for main-  
 course  
 untries,  
 -ferable  
 ts of a

village, suitable buildings, and arrangements for feeding and maintenance  
 are required

(e) Provision of social services—These services are needed to aid  
 patients themselves and the dependants of patients, particularly of isolated  
 patients, who may be left unprovided for. Small grants for the maintenance  
 of patients or  
 the supervisi  
 activity of su  
 healthy child  
 securing of employment for such persons

(f) *Provision of institutional accommodation for disabled non-infectious cases*—A considerable number of persons of this type are usually found. They are non-infectious, but because of the presence of deformities of hands and feet, trophic ulcers, etc., they are permanently

and such facilities should be provided

(g) *The organization of suitable propaganda to create the public opinion necessary for the success of the measures.*—This matter is of vital importance

(h) *Medical training*—Thorough training of the medical staff and practical instruction should be included in the ordinary pre-graduate medical curriculum, but centres of thorough post-graduate training are also needed

can play in such work, etc.,

d, but it is certainly advisable that the

and their dependants

In many countries where leprosy is common, the inauguration of a complete scheme of leprosy control along the above lines is impracticable, and in such circumstances an attempt should be made to concentrate on certain parts of the work which are of the greatest importance. It may for example be impossible to isolate all the infectious cases, and in such circumstances it is best to concentrate on preventing contact between infectious cases and children and young people. Infectious persons living in

surveys, which may

indication of the effectiveness or otherwise of measures adopted may be obtained by a demonstration of the presence or absence of a fall in the incidence of leprosy in children on periodical examination of all school children in the areas. In some countries, the reduction in the incidence of leprosy has been demonstrated by the fall in the incidence in young men reporting for compulsory military service

The results of compulsory isolation measures have varied markedly. In some countries, for example Norway, where the serious leprosy problem of sixty years ago has almost entirely disappeared and where public opinion gave strong support to the measures the results appear to have been excellent. In some other countries, particularly where public opinion has not given the necessary support the laws have been evaded and the measures have met with little success. In some countries, Japan and the Philippine Islands for example, a moderate degree of success appears to have been attained, but the work has not yet continued for sufficiently long to make possible a final judgment of its effectiveness. In Brazil a comprehensive scheme of leprosy control has recently been inaugurated, but it is too early to judge its results.

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**Introduction**—There are at least three tropical syndromes that have been given the status of named diseases which are caused by spirochaetes morphologically indistinguishable from the parasite of syphilis they are yaws pinta and bejel. All three are looked upon as modified forms of syphilis by some workers and as distinct diseases by others. They have many common features but perhaps the most important is that they are all three non venereal in origin.

There are probably other allied similar or identical diseases in other primitive and isolated populations. An example of such a condition is *Irkintja* of Central Australia recently described by Hackett (1936) who believes that the condition is identical with or at least closely related to yaws. In this condition there are early lesions similar to those of yaws usually in childhood and later gangosa boomerang leg and keloid scarring.

## YAWS OR FRAMBÆSIA

**Definition**—Yaws or frambæsia (French *framboise* = raspberry) known as *pian* in the French colonies and by many other local names elsewhere is a contagious disease resembling syphilis but non venereal in origin occurring mainly amongst aboriginal populations in the tropics.

characterized in its florid stage by multiple granulomatous lesions of the skin and later by a variety of lesions of the skin subcutaneous tissues and bones it is caused by a spirochaetal organism *Treponema pertenue* that is readily recoverable from the cutaneous lesions

**Historical**—It is not possible to identify definitely as yaws any of the skin diseases that are mentioned in ancient writings though several would pass as this disease

century

### EPIDEMIOLOGY

**Geographical distribution**—It has a wide tropical distribution and all the more important endemic centres are within the true tropics. It occurs in Central and South America in the West Indies extensively in equatorial Africa including the Sudan and Abyssinia in India Burma Ceylon Indo China Malaya and the East Indies generally and in Northern and Central Australia and certain Pacific islands. The most important sub tropical endemic foci are in Algiers and Tripoli in North Africa in Assam in India and in northern Burma.

In India it is much more widespread than is generally supposed occurring in Cochin Travancore Hyderabad the Central Province Chota Nagpur Bihar Santhal Parganas Chittagong Hill Tracts Manipur Cachar and several other places in Assam. Nowhere however has it assumed serious epidemic proportions and spread to the general populations of the plains of India.

countries where conditions are particularly suitable for its spread and die down or disappear when all susceptible persons (i.e. the children born since the last epidemic wave and the few adults who previously escaped infection) have been infected.

**Epidemiological features**—It is a disease of rural districts rather than towns. The incidence of the disease varies considerably. In certain isolated islands and other primitive populations practically every individual becomes infected sooner or later and usually sooner than is in childhood. In some tropical countries in equatorial Africa for example the disease is a very serious public health problem (e.g. over 300 000 persons were treated within a few years in the Belgian Congo which has a population of over 10 000 000).

or cases treated annually will amount to only a few hundred at a generous estimate.

The tropical distribution suggests that temperature is an important factor. Experience has shown that when a case is imported into a temperate country the infection does not spread. It has been found in India that the hill folk who tend to get the disease when they come down to the foot-

hills or into the hot, humid plains, do not take the disease back to their own villages if these are situated at any great height

**Humidity** is also important, and most of the endemic countries enjoy a high degree of humidity for a considerable part of the year, and luxuriant vegetation, however, the disease also occurs in Algeria and Tripoli which are relatively dry countries, as well as being outside the tropics

**Racial distribution**—In its natural form, it is a disease that is confined almost entirely to primitive peoples. This is most strikingly demonstrated in India, where it occurs amongst primitive hill folk, but seldom spreads to any extent amongst the plains' population (*vide supra*). This is almost certainly not due to personal susceptibility or immunity, as the disease is easily transmitted experimentally to individuals of any racial type but probably to the habits of the people who have a low standard of personal cleanliness, and live and sleep in primitive huts closely huddled together

to the

but a

it, mothers frequently contracting the infection from their children. In highly endemic areas, children usually contribute at least 90 per cent of the cases but in isolated communities where the infection is reintroduced at longer intervals a large proportion of adults will become infected. All contagious infections tend to spread more rapidly amongst children on account of their habits, but the most important influence in these cases is undoubtedly the immunity acquired by adults during previous outbreaks

Most writers report that males are more commonly infected than females. This is probably due to the greater freedom allowed male children. Chambers (1938) points out that in Jamaica the only age groups in which females predominate is from 20 to 29 years, this is an age at which women would be closely associated with infants and children and would be likely to be infected from them

## ÆTIOLOGY

**Historical**—Castellani in 1905 first isolated from yaws lesions an organism indistinguishable from the organism of syphilis, and named it *Spirochæta pertenue*, both these organisms were later placed in the genus *Treponema*

**The causal organism**—*Treponema pertenue* is a very slender (0.25 microns) spirachætal organism, from 8 to 18 microns in length, it has from five to a c  
1 micron  
flagellum  
morphologically identical with *Treponema pallidum* the causal organism of syphilis

**Culture and animal inoculation**—Culture of this organism was claimed by Noguchi and later by Hats, the former grew it in ascitic fluid to which kidney tissue had been added, anaerobically. Most other workers have failed to satisfy themselves that they have produced a true culture, and at any rate the procedure is not a practical diagnostic method

Successful inoculation has been produced in man higher apes monkeys, and rabbits, in the two latter animals only local lesions are produced

**Distribution in the tissues**—The spirochæte is found in the primary and secondary skin lesions in the spleen and in the bone marrow their presence in the blood has been demonstrated by inoculation

**Transmission**—This takes place by means of direct contact the organism from the exudate of a lesion entering the new host through an abrasion although possibly an invisible abrasion in his skin Whenever the point has been carefully investigated a history of close contact with some person with florid lesions has been obtained in almost every case and when mothers are infected by their infant the common sites of the primary lesion are on the breast at the bend of the elbow or on the hip places where direct contact most commonly occurs The mechanical transfer of infection by means of flies is

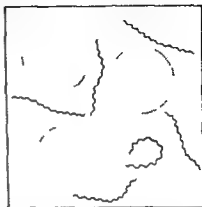


Figure 141 *Treponema pertenue*

experimentally incriminated as a mechanical transmitter in Jamaica Certain species of *Musca* have also been shown to be potential mechanical carriers of viable spirochætes but a biological cycle in any insect has never been seriously suggested

Man is the only known reservoir of infection

Congenital transmission never occurs

**The relation of the causal organism of yaws to that of syphilis**—This is a problem on which much work has been done during the last four decades without any final conclusion yet being reached

Morphologically the organisms are identical culturally no definite differences have been established serologically in the antigenic structure of the organisms common elements but also distinct differences have been shown to exist in animals readily distinguishable lesions are produced by these two organisms and in man there are marked differences in the two diseases they cause

Whether syphilis is a specialized form of yaws that has in the course of years undergone some change through being transmitted venereally amongst people that has lost its passage amongst heavy malarial they both arose and each developed demic interest far greater than same organism *Treponema per*

**Immunology**—Immunity to superinfection is not immediate and complete but it appears to take several months or even years to develop and

if early treatment is given reinfection becomes possible. Many cases of syphilis have been reported in individuals who have or have had yaws and conversely yaws has developed in syphilitics but there appears to be little doubt that populations that have been heavily infected with yaws enjoy some degree of immunity from syphilis. The reverse is probably true but not so easily demonstrated unless one takes the view that the relative immunity to yaws of towns folk in countries where yaws is common in the rural districts is due to the heavy syphilization of the town dwellers but this argument cannot be universally applied.

As in

with syphilis gives complete  
tion only gives partial pro-

The Wassermann and Kahn reactions become positive three to four weeks after the appearance of the primary lesions and are constantly positive after about the eighth week they remain positive for several years or as long as the infection is active. Those affected with yaws in early childhood usually lose their positive serum reactions after puberty so that whenever positive results are obtained in such persons they may usually be taken as evidence of a superimposed syphilis infection.

#### PATHOLOGY

The spirochæte gains entry through an abrasion or possibly even through the unbroken skin and enters the deeper layers of the epidermis where it multiplies producing a cellular (polymorphonuclear and plasma cell) reaction and œdema. The proliferation of the cells of the malpighian layer causes both a downgrowth of the interpapillary processes and is also a general upward growth that pushes up and eventually splits the stratum corneum into lamellæ between which fibrinous coagula form. There is also increased vascularity plasma cell and lymphocyte infiltration and some proliferation of the reticular cells of the papillæ. The spirochætal infection is mainly confined to the epidermis but eventually spreads to the surrounding lymph channels in the dermis and finally reaches the blood when generalization of the infection occurs.

From the moment of entry of the spirochæte the lesions of this first stage take three to four weeks to develop and after generalization has taken place there is usually an interval of two to three months before the secondary lesions appear these are multiple and appear on many parts of the body surface. The typical secondary yaws lesion is similar to the primary lesion described above.

After a much longer interval up to several years a third group of lesions may appear typically they are gummatous inflammatory lesions of the subcutaneous and other tissues that may lead to gummatous ulceration of the skin to fibrotic tumours in the skin or subcutaneous tissues especially around the joints to gumma and rarefaction of the bones and/or to diffuse keloid like formations of the skin.

It is suggested that the tertiary lesions are of the nature of an allergic reaction.

Some writers describe tertiary lesions of the viscera and the arteries similar to those of syphilis but the authenticity of such lesions seems doubtful and most observers agree that the lesions of yaws are mainly epiblastic that is to say affecting the skin and bones in contrast to syphilis.

in which the causal organism is panblastotropic that is it affects the tissues of all three embryonic layers

The lesions that occur can thus be placed in three groups the primary or initial lesions ( mother yaw ) the secondary or lesions of the generalised stage and the tertiary lesions or sequelæ Between these three stages

### SYMPTOMATOLOGY

The clinical picture corresponding to these three pathological stages will be considered under three separate headings —

**The primary stage**—There is usually a single lesion but it is possible for there to be more than one if infection occurs at two places After

single lesion an inch or even two inches in diameter There is usually an area of hyperæmia around the lesion and in dark skinned subjects there may be a halo of hypopigmentation around this The lymph nodes in the neighbourhood are often enlarged and slightly tender The primary lesion is sometimes pruritic and in other cases painful but usually it is both painless and non irritating

In some cases it is not possible to find any evidence of an initial lesion and in others a maculo papular or even a macular spot takes the place of the granulomatous initial lesion

This initial lesion may continue to develop and may still be active when the secondary lesions appear but it usually then tends to heal or on the other hand it may heal early so that there is only a scar to be seen when the second stage commences

This initial lesion is apparently not usually accompanied by any constitutional symptoms it is not however possible to be dogmatic on this point as the people who usually suffer from this disease are not very intelligent and would probably not notice or at least not report slight malaise

The site of the primary lesions will vary according to circumstances depending as they do on the one hand on abrasions and on the other on

lesions are very rare and are placed as low as 2 per cent in some populations

**The Secondary Stage**—The secondary lesions appear from six weeks to three months after the full development of the initial lesion The onset



of the secondary stage is often associated with mild constitutional symptoms, a low fever, not often above 100° F, joint pains, pains in the bones and general malaise

A large variety of secondary lesions are described, and in the textbooks these make a formidable array that must alarm and confuse the student. However, the pathological processes that produce these lesions are, qualitatively at least, the same, although they may vary in number, in distribution, and in the extent to which they progress before resolution, as well as being influenced by such variable factors, as, for example, individuality and racial differences in skin texture

The individual foci may produce very minute papules with little keratinization and, if these are arranged in groups, they will give the appearance of macules, or, if they are slightly larger and very numerous, that of a lichenous rash. When these lesions resolve, they desquamate, producing the furfuraceous desquamation that is described. If there is a little more keratinization, a papular or papulo-macular eruption will result. The majority of these papules will subside, but some will continue to develop and the typical papillomatous frambœside, very similar to the initial lesion, will appear. These yaws papules sometimes develop in the form of a ring with an area of unaffected skin in the centre, this particular form is given the name ringworm yaws.

Finally, when these lesions develop in the skin of the palms or soles on account of the great thickness of the epidermis there, the clinical results are very different from those in other parts of the body. Many types of plantar and palmar yaws are described, and given various and often vernacular names but amongst the commonest types are the vesicular and papular eruptions that lead to separation of the superficial layers of the

throughout  
and crippling  
invasive granu-  
lar deformity

of the feet known as *clavus*

The lesions appear in crops, so that there will often be lesions in all stages of development present at the same time. This will also mean that the order of development may not seem to be consecutive and, for example, the furfuraceous rash may appear after a typical frambœside (from an earlier crop) has already developed.

Thus, there are three types of secondary lesion, the early diffuse frambœsides of several types, the typical papillomatous frambœside, and the late plantar or palmar lesions.

**Sites**—The diffuse lesions, that is, the papular eruption, the furfuraceous rash, etc., appear mainly on the trunk and the limbs whereas the typical frambœsides appear most commonly on the face, the limbs and the buttocks, also on the trunk, neck, and perineum but the scalp is very seldom affected, the junction of skin and mucous membrane, (e.g., around the anus, the mouth, and the alæ nasi) are the most favoured sites.

**Progress.**—The fully-developed typical papillomatous frambœsides vary from the size of a pea to that of a large walnut (3-4 cm), but they will usually be present at all stages of development and healing. They may heal within a month or so, or persist for years. When they heal, either spontaneously or as a result of treatment, they leave a white scar, this scar may become pigmented in the course of time or it may persist for life.

**The Tertiary Stage.**—Most of the lesions in this stage owe their association with yaws to the fact that they are common lesions in populations

These lesions may appear at any time from one year to twenty years after the appearance of the secondary lesions. Amongst the earliest and most typical tertiary lesions are **juxta-articular nodules**. These are hard, fibrotic swellings in the subcutaneous tissue around the joints, varying in size from a pea to a pigeon's egg. They are usually attached to the ligamentous tissues of the joint or tendon sheaths, but the skin is freely moveable over them—at least at first. Later, probably as the result of trauma, it may become fixed. They are not normally painful but from their position (usually on the outer side of the joint), are very liable to damage. The knees and ankles are the commonest joints affected, but the nodules may occur around almost any joint, and similar fibrotic swellings are sometimes found in the subcutaneous tissue in other parts of the body.

Gummata develop in the subcutaneous tissues, and eventually ulcerate through the skin causing chronic septic ulcers.

There are several types of bone lesion. A soft painful swelling of the periosteum, particularly of the tibia and ulna that occurs relatively early in the disease is often classed as a secondary lesion. There is also an

spontaneous fracture a common occurrence

There remain two clinical syndromes that are now recognized as being usually, although perhaps not always, sequelæ of yaws infection, namely **gangoza** and **goundou**. The former usually occurs in adults who have suf-

ferred from yaws in childhood, but the latter often appears at an earlier date and affects children. The evidence for the ætiological connexion between these diseases and yaws is not clear, but in only a few cases the lesions which they may be associated with are of a logical factors.

**Gangosa, or Rhinopharyngitis Mutilans**—This is a condition in which there is ulceration of the mucous membrane of the nasopharynx and nose, which involves and eventually destroys the soft tissues, cartilages, bones and eventually the skin, working from within outwards, until the whole mouth nose passage is destroyed, leaving a large fungating cavity with the remains of the process occur in which the process is halted, either spontaneously or as a result of treatment, before the destruction has been complete. The condition was at one time associated

hood

Somewhat similar conditions may be produced by rhinoscleroma and by espundia (qv)

**Goundou.**—In this condition, there is a bony exostosis of the nasal processes of the upper maxilla, usually bilateral. It is usually associated with severe headaches, some nasal obstruction, and a sero-purulent and sometimes blood tinged discharge from the nose. The skin over the exostosis is normal and freely movable. The tumour may obstruct the lacrymal ducts and interfere with the line of vision, but does not encroach on the orbit or otherwise affect the sight.

#### DIAGNOSIS

**Clinical**—The typical yaws lesion is so characteristic that it is unlikely to be mistaken for other conditions, but many of the other less typical lesions may well be, and it will often only be possible to diagnose their nature clinically by their association with the typical frambæside.

**Laboratory**—From the primary and from many of the secondary lesions, especially from the frambæside it is possible to recover the spirochæte without much difficulty.

the Indian  
by Tribon-  
hese stains

(see p 242)

**Differential diagnosis**—Syphilis and leprosy are probably the two diseases with which yaws has been confused most frequently in the past, but the protean nature of the manifestations of yaws make it possible to confuse the individual lesions with those of almost any skin disease and of many ulcerative conditions, e.g., pityriasis rosea, versicolor and pilaris, lichen planus, acne vulgaris, psoriasis, ichthyosis, impetigo contagiosa, tinea, eczema of various forms, lupus erythematosus and vulgaris,

oriental sore and South American leishmaniasis    *ulcus tropicum*, yeldt sore, and septic varicose and malignant ulcers

The joint pains in the earlier stages and the juxta articular nodules  
' ' ' ' ' ' ' ' the juxta  
' ' ' ' ' ' ' ' other parts

TABLE XIV

The following table gives the main points of differentiation between yaws and syphilis —

	YAWS	SYPHILIS
<i>Epidemiology</i>	Primitive people Children under 14 years Seldom venereal Never congenital	Civilised people Adults Usually venereal May be congenital
<i>Tropism</i>	Epiblastotropic	Panblastotropic
<i>Primary lesion</i>	Extra-genital Variable but usually typical fram boeside Glandula involvement—not con stant and glands soft Wassermann & Kahn reactions — negative	Genital Typical indurated chancre Commonly abtorty en largement Often positive
<i>Secondary stage</i>	Typical framboeside and furfuraceous desquamation Mucous membranes not affected Eyes unaffected  Alopecia —unknown Constitutional symptoms —slight Wassermann & Kahn reactions — positive	Rash sore throat etc Often affected Iritis common other eye lesions may occur May occur May be marked Positive
<i>Tertiary stage</i>	Lesions superficial and obvious, trou blesome and crippling non fatal  Nervous and cardio-vascular sys tems —not affected (according to most authorities) Blood Wassermann reaction —usu ally positive but may be negative	Lesions mostly of vis cera subtle often fa tal Both affected  Always positive
<i>Para lesions</i>	Do not occur (according to most au thorities) CSF Wassermann reaction —never positive	Tabs and GPI may occur Often positive
<i>Treatment</i>	Does not respond to mercurial treat ment	Will respond to mercurial treatment

## PREVENTION

This disease is essentially one of uneducated populations amongst  
these

is a definite one first principle in prevention This may however be too idealistic or at least too long term a policy for most circumstances and organized wholesale treatment of the population will in most circumstances be the best method to adopt. How

this treatment can be provided will depend entirely on the special circumstances. Where the people are easily accessible, a system of permanent hospitals and dispensaries, with doctors, nurses, and health visitors, can be arranged, but for isolated communities it will be necessary to have itinerant units that can move from centre to centre. It has been shown that, though a full course of injections may be necessary to ensure a complete cure (*vide infra*), by giving even one or two injections to each infected individual it is possible to reduce the disease in a population very considerably, as well as to provide much relief to the infected individuals.

It is unnecessary to discuss such obvious, but in the circumstances totally impracticable, measures as isolation and early treatment of abscessions.

### TREATMENT

This can be considered under the four headings, (a) general, (b) local, (c) specific, and (d) subsidiary.

a) **General treatment**—There is little that need be said about general treatment, it is obvious that a well-balanced nourishing diet, suitable clothing that can be changed daily, warm baths, hot, demulcent drinks, regulation of bowels, and so forth, are ideal recommendations, but in the conditions under which yaws usually has to be treated it will be impossible to apply them and one will usually be quite satisfied if it is possible to give the specific treatment to all those that require it.

b) **Local Treatment**—More rapid healing will certainly be brought about if the lesions are bathed in some antiseptic lotions, the writer has used mercurial lotion and acriflavine, 1 in 1000, but probably some of the newer antiseptics will be more effective. For applications that can be given to the patient, the most useful are those that prevent infection of the external surface. These will have a beneficial effect if the patient is kept clean and the external surface is kept dry.

c) **Specific treatment**—The specifics are arsenic and bismuth. There are three different lines of treatment which can be adopted according to the varying circumstances, or perhaps judiciously combined, namely (i) intravenous or intramuscular arsenicals, (ii) intramuscular, bismuth and (iii) oral arsenicals.

(i) The most rapid and dramatic results can be obtained by neosalvarsan (e.g. neosalvarsan) injections, in doses up to 0.90 gramme for men, 0.60 g for weak or small men and for women, 0.30 g for a child under 10 years, and 0.10 g for a child under two years, or, on a weight basis, 0.01 g (one centigramme) per kilogramme of body weight. A distinct improvement will be produced by the first injection, and complete disappearance of primary or secondary lesions after two or at the most three, injections. The secondary, or more general opinion now is that the dosage should be 0.14 milligrammes per kilogramme of body weight.

some, any of the preparations of value in this disease are used extensively in recent years. 14 milligrammes per kilogramme of body weight.

*Fourth picture shows the result of treatment*



Fig 1



Fig 2



For young children, and when large numbers of persons have to be treated in a short time or under difficult circumstances, intramuscular injections may be preferred by some workers. The usual precautions regarding the administration of these toxic drugs will, of course, have to be taken.

(ii) *Treatment by injections*—The following preparations (dose up to 0.2 gramme), sodium potassium bismuth tartrate suspension in oil (dose up to 0.3 gramme), and precipitated bismuth suspended in oil to make a 10 per cent suspension (dose up to 0.2 gramme), have all been used with good effect. The first injection should be about half the maximum dose and the dose should be increased by 0.5 c.c. at each injection. For children are given correspondingly smaller doses.

A watch must be kept for stomatitis and albuminuria.

Treatment with bismuth is unque-  
namine, but this form of treatment is  
cheaper. There are several useful  
e.g., bismotab, and neptrepol, which  
to be treated, but by their use on a  
low cost is lost.

(iii) *There are several safe and effective arsenical preparations* that  
can be given by mouth, e.g. stovarsol and carbarsone. These must be given  
in the full therapeutic dose, 0.25 gramme twice daily for an adult, for 10  
days,  
month  
with  
the parenteral arsenic or bismuth.

Several combinations of these three forms of treatment have been  
suggested, but probably the most effective is a course consisting of two in-  
travenous neoarsphenamine and six intramuscular bismuth injections at  
weekly intervals, the arsenic and bismuth injections being given con-  
currently on the first two occasions, the cost of such a course is not very high.

To summarize, for efficiency parenteral arsenic is the drug of choice  
for cheapness parenteral bismuth, and for utility the special arsenical prepa-  
rations by mouth.\*

Whatever the treatment given, the aim should always be the reversal  
of a positive Wassermann or Kahn reaction.

(d) *Subsidiary treatment*—For the tertiary lesions, some workers have  
used potassium iodide by mouth in large doses, either alone or in com-  
bination with arsenic and/or bismuth, they claim that a more rapid resolu-  
tion is brought about by this means.

For some of the tertiary lesions, e.g. the juxta-articular nodules, the  
contractures, and goundou, surgical treatment will also be indicated.

*Prognosis*—Even when the condition is left untreated, spontaneous  
resolution will occur in a certain percentage of cases in both the primary  
(but probably rarely) and in the secondary stage, and the latter lesions  
usually last from six months to two years. In neither of these stages does  
death ever occur as a direct result of the disease, and in both proper treat-  
ment will always produce a cure.

\* For penicillin therapy in yaws, see addendum, p. 542.

The lesions of the third stage may be life long in their effect and even if treatment is given there will usually be some permanent disabilities here again however death will seldom occur as a direct result of the lesions although quite often as an indirect one. Death from septic pneumonia occurs sooner or later in most cases of gangosa.

## PINTA

**Definition**—Pinta (mal del pinto or carate) is a contagious disease that occurs in certain tropical countries in the western hemisphere. It is

teum

same country

## EPIDEMIOLOGY

**Geographical distribution**—The disease has a limited tropical distribution in the western hemisphere. The main countries affected are Colombia (4 per cent of the population) and Mexico (11 per cent) but it also occurs in Cuba and other islands of the West Indies, Venezuela, Ecuador, Peru, Brazil and Central America. The endemicity of the disease has not been established in the eastern hemisphere though isolated and questionable cases have been reported from time to time in northern Africa, Iraq, India, Malaya and the Philippines.

The age incidence appears to vary in different countries and even in

so that superficial estimates indicate that the largest number are in the third and fourth decades whereas smaller and probably more accurate ones indicate an earlier age incidence.

People of the dark skinned races seem to be more easily infected. This is apparent in mixed populations.

## ÆTIOLOGY

**Historical**—The causal organism *Treponema carateum* was discovered by Doctors Trana and Armenteros, in the exudate from lesions and in the associated lymph



For young children, and when large numbers of persons have to be treated in a short time or under difficult circumstances, intramuscular injections may be preferred by some workers. The usual precautions regarding the administration of these toxic drugs will, of course, have to be taken.

(ii) The effect of bismuth injections is not immediate, at least six injections at weekly intervals should be given but distinct improvement will follow a smaller number. Bismuth salicylate in a 10 per cent solution (dose up to 0.2 gramme), sodium potassium bismuth tartrate suspended in oil (dose up to 0.3 gramme), and precipitated bismuth suspended in oil to make a 10 per cent suspension (dose up to 0.2 gramme), have all been used with good effect. The first injection should be about half the maximum dose and the dose should be increased by 0.5 ccm at each injection, children are given correspondingly smaller doses.

A watch must be kept for stomatitis and albuminuria.

Treatment with bismuth is unquestionably inferior to that with arsphenamine, but this form of treatment has the advantage of being very much cheaper. There are several useful proprietary preparations of bismuth, e.g., bismotab, and notrepol, which will be convenient if a single case is to be treated, but by their use on a large scale much of the advantage of low cost is lost.

(iii) There are several safe and effective arsenical preparations that can be given by mouth, e.g., stovarsol and carbarsone. These must be given in the full therapeutic dose, 0.25 gramme twice daily for an adult, for 15 days, if further dosage is required, an interval should be allowed of about a month before a second course is started. Good results have been obtained with this treatment, but these oral drugs are definitely less effective than the parenteral arsenic or bismuth.

Several combinations of these three forms of treatment have been suggested, but probably the most effective is a course consisting of two intravenous neoarsphenamine and six intramuscular bismuth injections at weekly intervals, the arsenic and bismuth injections being given coincidently on the first two occasions, the cost of such a course is not very high.

To summarize, for efficiency parenteral arsenic is the drug of choice, for cheapness parenteral bismuth, and for utility the special arsenical preparations by mouth.\*

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For some of the tertiary lesions, e.g., the juxta-articular nodules, the contractures, and goundou, surgical treatment will also be indicated.

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**Discussion**—Much has been discovered about this disease during the last few years.

It has been found that the disease is managed to evade investigators in some of the countries where it is endemic.

Tertiary manifestations and sequelae of pinta are really caused by the *Trep. carateum* as is shown in view of the fact that syphilis or yaws are usually endemic in the same country.

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A watch must be kept for stomatitis and albuminuria.

Treatment with bismuth is not a cure.

to be treated, but by their use on a large scale cost is lost.

(iii) There are several safe and effective arsenical preparations that can be given by mouth, e.g. stovarsol and carbarsone. These must be given in the full therapeutic dose 0.25 gramme twice daily for an adult for 10 days, 1 month with the paraffin oil solution in capsules.

Several combinations of these three forms of treatment have been suggested but probably the most effective is a course consisting of two intravenous neoarsphenamine and six intramuscular bismuth injections at weekly intervals the arsenic and bismuth injections being given conjointly on the first two occasions. The cost of such a course is not very high.

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For some of the tertiary lesions e.g. the juxta articular nodules the contractures and goundou surgical treatment will also be indicated.

**Prognosis**—Even when the condition is left untreated spontaneous resolution will occur in a certain percentage of cases in both the primary (but probably rarely) and in the secondary stage and the latter lesions years. In neither of these stages does the disease and in both proper treatment.

for referring to the former as tertiary and it is questionable if the latter are really pinta lesions, occurring as they do in populations in which both yaws and syphilis are common

**Diagnosis.**—*Treponema carateum* can be found in every case from the

depigmented stage develops. Thus neither the Wassermann reaction nor the finding of spirochaetes helps in the differential diagnosis

From a clinical point of view, the difference between yaws and pinta is that the latter never causes true ulceration, nor the tertiary lesions commonly associated with yaws, although opinion on this latter point is not unanimous. Pinta is also confined almost entirely to the dark-skinned races

Only gross ignorance of the clinical picture of both diseases could lead to confusion between pinta and leprosy

#### PREVENTION AND TREATMENT

The only effective prevention measures are education and treatment as in the case of yaws

The earlier lesions respond rapidly to anti-syphilitic treatment (also see p. 534) but a full course is often necessary to reverse a positive Wassermann reaction. The atrophic and pigmented lesions will seldom respond

leucoderma

#### BEJEL\*

**Introduction.**—In 1928, while practising medicine in Deir el Zor, Syria Hudson drew attention to a non-venereal mucocutaneous treponematosis encountered among the nomadic tribes in Arab countries. This condition is known as *bejel* in Iraq and Syria, *firjal* and *latta* in Palestine, *laghout* in Lebanon and *jarar* in Trans-Jordan

Hudson (loc. cit.) at first described the disease as a distinct entity, but has modified his views recently (Hudson 1937, 1938), and is now inclined to support Hasselmann's view. He (Hudson 1941) has gone even further and considers that it is a modified form of syphilis. From this point of view he considers that syphilis and *bejel* are two distinct clinical entities. It is not unlikely that originally all four causal organisms developed from a common source, but it seems more probable that *bejel* was historically the earliest of the treponematoses from which these other diseases evolved

**Geographical distribution.**—Whereas yaws is a tropical condition which is always associated with abundance of vegetation, humidity and

\* By Harry Senekjic M.D. M.S. Assistant Professor of Tropical Medicine Tulane Medical School. The published papers on this disease are very contradictory and as Dr. Senekjic has had at least six years' experience in the countries where this disease occurs the author asked him to contribute this section.



nodules of a case of pinta in Havana, Cuba, in August 1938. This finding was con-

The causal organism, *Treponema carateum*, is morphologically very similar to *T. pallidum*, with measurements, out 17 microns, a flexible spiro at about one early papular lesions, but are very scanty in the later dyschromatic and depigmented lesions.

As the exudates from all the early lesions contain treponemata which, as in the case of yaws, can enter the new host through a small skin abrasion direct transmission is possible, therefore direct contact is probably the usual method of transmission. But it has also been shown that certain flies, e.g. *Hippelates pallipes* and *Simulium hæmatopotum*, are capable of mechanically conveying viable spirochaetes, and it is therefore possible that these and other flies also play some part in transmission, in places where

#### SYMPTOMATOLOGY AND PATHOLOGY

After an incubation period of 7 to 20 days a small papule appears at the point of entry of the infection. Within a few days further papules appear around the first one, and an erythematous-squamous patch develops. This scaly patch is slightly raised above the skin surface and is variously shaped but usually more-or-less round and anything up to an inch and a half in diameter. It takes four to seven weeks for it to attain full development, when it becomes a chronic, irritating but non-ulcerating lesion.

The particular pathological characteristic of the pinta lesion is at first a stimulation of the cells of the melanoblastic layer and later their destruction, so that there is at first hyperpigmentation, a characteristic dark coppery pigmentation of the skin, usually on the face, but also on other parts of the body, and later, atrophic lesions with leucoderma, or vitiligo. The explanation for the dyschromatic effects that are sometimes seen is variation in the differences in the isms, for it has not produce the the palms and o-purulent dis-

charge from these the causal organism can be seen

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papules appear on the trunk extremities groin and genitalia and develop into circinate and rarely roseolar eruptions. As there is never a history of anything corresponding to the primary chancre of syphilis it seems probable that these constitute the primary lesions.

There are no constitutional symptoms and no pain or pruritis in association with these early lesions and apparently the health of the child is not impaired. These lesions disappear spontaneously without leaving any scar and often without any treatment.

A latent period is followed by the appearance of the late lesions which are usually ulcerative in character. A small erythematous patch appears in the soft tissues of the mouth this breaks down and spreads to the soft palate tonsil or pharynx so that swallowing becomes painful. Leucoplakial patches may be observed in the mouth. After several months the lesion heals with the formation of scar tissue. Sometimes the process extends to the larynx and produces changes in the voice or hoarseness or even stridor due to the contraction of the cicatrix. Similarly the ulcerative lesions of the nose may destroy the soft tissues and even erode through the hard palate into the mouth and maxillary sinuses producing a gangosa like condition and rarely paranasal swellings resembling goundou develop.

The characteristic skin lesions begin as papules and then ulcerate these granulomatous ulcers heal in one place while spreading in another and at times fungating masses result that become covered with crusts and exude a sero sanguineous or purulent discharge.

Hyperkeratosis of the soles of the feet either localized at sites which bear weight or generalized with extensive fissures are common findings. There are similar lesions of the palms. Sometimes depigmented areas appear on the skin and there may be alopecia (Hudson 1936).

Periosteitis and osteitis especially of the long bones frequently occur patients complain of throbbing bone pains and sometimes the small bones of the hands are involved. Juxta articular nodules around the knee ankle and back are seen. These are painless movable hard masses which do not have any tendency for ulceration but may become fibrosed (Hudson 1935).

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Apparently there are no cardiovascular symptoms but occasionally

general paralysis are rare among Arabs.

#### TREATMENT

The specific treatment of choice is neoparsphenamine. It must however be remembered that the Arab cannot tolerate large doses of arsenicals. Bismuth comes next in its effectiveness while mercury also gives very satisfactory results. A much shorter course of treatment than that given for syphilis is necessary.

rainfall, bejel occurs in dry and hot climates mainly in desert areas. It has

nomadic Arabs, though up to the present no confirmatory reports have been received from these areas.

### EPIDEMIOLOGY AND TRANSMISSION

A very high percentage of the people of all social strata in infected nomad Arab tribes suffer from the disease. It is usually acquired in early infancy or childhood, but when children escape infection, they will frequently become infected in later life. Although venereal transmission is possible, the infection is usually transmitted non-venereally. Promiscuous sexual intercourse is uncommon in these tribes, but cups, glasses, plates and towels are shared freely by the members of not only one, but of several families.

During certain seasons flies are very prevalent and, just as yaws is apparently transmitted by *Hippelates pallipes* and pinta by *Simulium hæmatopotum*, so bejel may be transmitted mechanically by house-flies.

Unlike syphilis, but like yaws and pinta, bejel is never transmitted congenitally.

### ÆTIOLOGY

The causal organism is morphologically indistinguishable from *Treponema pallidum*, *T. pertenuis*, and *T. carateum* but, in the writer's opinion it is more flexible. The spirochæte is found easily in early lesions, but is very scanty in the late lesions, the former are presumably the most infectious. Attempts to infect rabbits, guinea pigs, and mice intradermally have so far failed.

**Immunity.**—There is no natural immunity to bejel, and persons of all ages and races are apparently susceptible, but immunity can be acquired through previous infection, thus, most adult Arabs are immune through infection in childhood. The Wassermann, Kolmer and Kahn reactions are constantly positive in this disease.

The question of cross immunity between bejel, and syphilis, yaws and pinta has not yet been settled, but the writer has seen syphilitic chancre develop in Arabs who had had bejel and who showed a positive Kahn reaction.

### PATHOLOGY

This has not been studied to the same extent as in the other treponematoses, but it is evident that this disease is an epiblastotropic one, like yaws and pinta, rather than a panblastotropic one, like syphilis.

The skin lesions are characteristically granulomatous ones.

### SYMPTOMATOLOGY

The initial lesions are usually in or around the mouth, however, in those rare cases where the infection is venereal the lesions are naturally on the genitalia. These initial lesions are usually patches which desquamate but do not ulcerate. The usual location is the lips, angles of the mouth, tongue, mucosa of cheeks, rarely the glans penis, labia, or mucosa of the vagina. At the same time, or sometimes after a short interval,

papules appear on the trunk extremities groin and genitalia and develop into circinate and rarely roseolar eruptions. As there is never a history of anything corresponding to the primary chancre of syphilis it seems probable that these constitute the primary lesions.

There are no constitutional symptoms and no pain or pruritis in association with these early lesions and apparently the health of the child is not impaired. These lesions disappear spontaneously without leaving any scar and often without any treatment.

A latent period is followed by the appearance of the late lesions which are usually ulcerative in character. A small erythematous patch appears in the soft tissues of the mouth this breaks down and spreads to the soft palate tonsil or pharynx so that swallowing becomes painful. Leucoplakial patches may be observed in the mouth. After several months the lesion heals with the formation of scar tissue. Sometimes the process extends to the larynx and produces changes in the voice or hoarseness or even stridor due to the contraction of the cicatrix. Similarly the ulcerative lesions of the nose may destroy the soft tissues and even erode through the hard palate into the mouth and maxillary sinuses producing a gangosa-like condition and rarely paranasal swellings resembling goundou develop.

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#### TREATMENT

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**Prevention**—The most effective means will be by education and propaganda amongst the tribesmen, combined with a treatment campaign particularly amongst the children. Bismuth is the most practical drug for this on account of its relatively low cost and long continued action, but arsphenamine is more potent.

### PROGNOSIS

This is good. In many cases a spontaneous clinical remission will occur without treatment, and the response to anti-syphilitic treatment is excellent.

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**Addendum**—Penicillin is very effective in the treatment of yaws and will very probably prove to be the drug of choice for any of these three spirochaetoses when cost is not important. A total dose of 500,000 units given over a period of 5 or 6 days will effect a cure.

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**Introduction**—There are many types of skin ulceration that will be encountered as frequently in a temperate as in a tropical climate specific ulcers *e.g.* syphilitic tuberculosis actinomycotic and glanders ulcers associated with systemic or blood diseases such as diabetes sprue pellagra sickle celled anæmia and purpuric conditions non specific ulcers associated with varicose veins and septic ulcers secondary to skin diseases wounds abrasions and insect bites

However skin ulceration is both commoner and more chronic in the tropics than in the temperate zones This is in part because many specific parasitic infections are peculiar to the tropics but also because insect bites and the subsequent self inflicted trauma so frequently cause breaches in the integument because the high temperature often associated with high humidity encourages the growth of bacteria on and in the skin and its glands and appendages and because there are so many systemic infections and dietary deficiencies to lower the tissues resistance to invasion The multiplicity of the predisposing conditions and superimposed infections tends to produce ulcers of such a wide variety that a description of all of them is out of the question

The ulcers especially associated with the tropics that have been described or will be described in other sections include the cutaneous leishmaniasis oriental sore (p 179) and espundia (p 191) leprosy (p 481) yaws (p 523) cutaneous amœbiasis (p 435) tularæmia (p 345) rat bite fever (p 237) tatusugamushi disease (p 275) and the venereal ulcerations lymphopathia venereum (p 562) and granuloma venereum (p 568) as well as the secondary ulcerations of bubonic plague and the rare cellulocutaneous type of septicæmic plague (p 335)

This leaves two tropical skin ulcerations that do not fall naturally into any other section namely *ulcus tropicum* or Naga sore and veldt sore

### ULCUS TROPICUM

**Definition**—*Ulcus tropicum* is a troublesome lesion that occurs in workers in humid tropical climates at least by an anærobic fusiform bacillus

\*)  
Id  
at

**Geographical distribution**—*Ulcus tropicum* occurs in many tropical countries but the majority of the earlier reports on this condition came from Africa and India It is also common in tropical America

### EPIDEMIOLOGY

It occurs almost exclusively in hot damp climates and amongst farmers and field workers It is more commonly reported amongst labour forces *e.g.* tea plantation workers in such countries but this is probably because of the financial loss to employers entailed as there is evidence that private cultivators also often suffer from the condition Recently a number

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\* The word phagedænic (literally meaning eating canker or spreading ulcer) is

ber of British and Indian soldiers in Assam have suffered from somewhat similar sores, but it seems questionable whether these sores have the same aetiology.

The disease occurs not only among men, but women and children are also susceptible in those population groups where both sexes work in the fields.

In the tea-estate labour forces in India, *ulcus tropicum* reaches its

There is a marked variation in the incidence from year to year in any one locality, this has been particularly noticeable on tea-estates.

### ÆTIOLOGY

A number of theories as to the cause of this condition have been put forward, with reference to which it is easier to be critical than constructive.

The subject can best be discussed under three headings, the predisposing factor, the specific organism, and the determining factor.

(a) *The predisposing factors.*—There has been a strong tendency in recent years to attribute tropical ulcer to dietary deficiency, in whole or in part. The present writer (Edwards 1934) disagrees with this view from the point of view of experience in Papua, where the disease should be considered as suffered more than

Papua in which dietary deficiency is incriminated have never been very convincing or very specific in their indications as to which particular dietary element is the determining one, several vitamins and calcium have been named. Further, many instances of the infection—natural, experimental and accidental—of well-nourished persons have been reported of the epidemiology and even probably,

Again, it would seem not unreasonable to suggest that debilitating diseases may reduce the individual's resistance against the invading organisms, and standard tropical infections such as malaria, dysentery and ancylostomiasis have naturally been selected, in fact at one time these ulcers were actually labelled 'malaria ulcers'.

(b) *The specific organisms.*—The frequency with which a fusiform bacillus alone or the fusiform bacillus plus a spirochæte are found in the wound again makes the case for the infection theory.

Without taking sides in this controversy, refer to the condition as fusospiro-

\* Charters (1943) has produced further evidence to support the dietary-deficiency theory. He considers that vitamin A is the deficient element.



chætosia. In India, we have found that the fusiform bacillus is constantly present and that there is always another organism almost equally prominent in the field, this is, however, not always a spirochæte but is quite often a diphtheroid. This view is not incompatible with the unitarian theory referred to above, as, in the instances in which there were no spirochætes in the ulcers, it may simply have meant that on account of some local condition in the ulcer all organisms were in the fusiform stage.

The proof of the causal association of these organisms is not complete as it has never been possible to induce an ulcer with a pure culture of any of them, although this has been done frequently with mixed organisms from an ulcer, and with a mixed culture of *Bacillus fusiformis* and

The fusiform bacillus is about 17 microns in length and 1 micron in thickness, it is fusiform in shape, as its name implies, and it stains well with Romanowsky stains, usually showing a slightly beaded appearance. It is gram-negative.

It is an anaërobe and can be grown on gelatin-serum agar. It would however, be surprising if in the many tropical countries in which an apparently similar ulcer appears there were not more than one specific organism concerned.

The Klebs-Loeffler bacillus has on several occasions been isolated from a clinically typical Naga sore.

(c) **The determining factors**—There seems to be very little doubt that some breach in the epithelium is essential to allow the organisms to gain entry. Four common causes are—(i) injury, (ii) dermatitis, (iii) insect or leech bite, and (iv) 'water sores' (ancylostoma invasion). The ulcer appears most commonly on the legs and feet at points most subject to injury in those who walk about bare legged, on areas of skin likely to be affected by dermatitis as a result of coming in contact with irritant plants, chemical manures, etc., or at points where hookworm larvae often enter and cause vesiculation. Panja and Acton (Acton, 1932) showed experimentally that it was easier to produce an ulcer on the leg than on the arm. In the latter situation, a sore formed but healed rapidly, whereas in the former it developed into a typical ulcer.

It is often found that occupational groups particularly subject to local injury, e.g. tea-garden coolies working amongst tea bushes suffer more than their fellow coolies who work in the factory, and even amongst Clements' Papuan natives (*vide supra*) the factor may have been occupation rather than diet.

**The source and transmission of the causal organism**—The fusiform organism is found infecting the mouth and other mucous membranes, but it also occurs widely in nature as a saprophyte and is commonly found in the soil. The ulcers appear in outbreaks in which a large number of persons are affected about the same time, but it has never been satisfactorily

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Insects have been suspected as vectors, but there is no indication that they act otherwise than as mechanical transmitters, the common house-fly and flies of the genus *Siphunculina* have been particularly sus-

pected. Flies of the latter group are very prevalent during the season at which these ulcers occur, and they are certainly attracted to purulent wounds but they have never been incriminated experimentally and some negative observations have been made. It is almost certain that flies could act as mechanical transmitters how far they are responsible for outbreaks is uncertain and there is little positive supporting evidence for the hypothesis.

Roy (1928) suggested that the bacillus probably remains in the soil just below the surface during the dry season and that when the first monsoon rains convert the surface soil into mud which is splashed and caked over the legs of the coolies or cultivators anaerobic fusiform bacilli, which are imbedded in the mud infect existing skin wounds. Later when the rains become heavy the bacilli are washed out of the soil. The present writer feels that this theory fits many of the known facts regarding the epidemiology of the disease. It seems quite possible that the variations in the incidence of *ulcus tropicum* from year to year might be accounted for by variations in climatic conditions or in the use of manures which will alter the soil flora.

#### PATHOLOGY

The fusiform bacillus is unable to establish itself without the cooperation of some other organism the membrane producing diphtheroids appear to be amongst the most suitable symbionts. The fusiform anaerobes multiply rapidly under the protecting membrane and establish themselves in subcutaneous tissues they have limited powers of tissue invasion but they produce a toxin that causes necrosis of the overlying skin and a cellular reaction in the surrounding tissues. Later there is granulation tissue formation at the edges and at the base of the ulcer under the layer of fusiform bacilli which form a thick mat immediately under the upper necrotic layer of the ulcer this granulation tissue is later replaced to some extent by fibrotic tissue. There is some indication that the individual ulcer is anatomically self limiting as the ulcer tends to be circular and not more than an inch or two inches in diameter its downward extension is limited by the first fascial layer that it encounters and its lateral extension by a ring of cellular reaction and eventually by the fibrosis that occurs. There are of course, occasions when two or several separate ulcers join to form a large and sometimes irregular shaped ulcer which may almost surround the leg interfere with the circulation and lymph drainage and cause painful oedema of the leg and foot. There is no evidence of haematogenous or lymphatic extension although the proximal lymph nodes may enlarge as a result of infection of the wound with septic organisms.

#### SYMPTOMATOLOGY

Small itching papules appearing at the site of an existing scratch or abrasion rapidly become necrotic and if the necrotic tissue is removed a small ulcer with undermined edges will be found underneath. The ulcer spreads rapidly and in a few days will have reached the standard size (*vide supra*) a circular ulcer from an inch to two inches in diameter. Other ulcers may meanwhile be developing in the neighbourhood these may remain discrete or may coalesce and form a large ulcer. In a large percentage of cases there is however only a single circular ulcer.

The ulcers are usually on the lower limbs on the dorsum of the foot at the ankle or instep or on the front of the leg a few inches above the instep they rarely occur above the knee.

Mild constitutional symptoms of a toxæmic rather than a febrile nature often accompany the ulcers. Even deep ulcers may not be particularly painful, provided they do not interfere with the blood supply or lymph drainage, but when this occurs the swelling, heaviness, and pain make the patient unable, or at least disinclined to do his work.

In those cases in which the Klebs-Loeffler bacillus has been found, the neuritic sequelæ associated with this infection will often be observed (see VELDT SORE).

The discharge is usually a reddish watery exudate that trickles continuously from under the necrotic membrane that covers the ulcer. The edges of the ulcer at first are undermined, but later become firm, fibrotic, and raised. The ulcer extends down to the first fascial layer or to the bone, but the ordinary tropical ulcer does not usually involve the bone or the joints, however, the danger to joints from the presence of a large open septic wound in their vicinity is obvious, and in many cases the septic infection does extend to the tendon sheaths and joints, producing a dangerous condition at the time and serious crippling afterwards.

The ulcers are usually very chronic but even without any special form of treatment most of them will heal in a few months time, in Assam, for example, when the rains stop and the weather becomes cool again. They leave a considerable scar. Any immunity built up can only be very temporary as it is not uncommon for a patient to suffer from these ulcers at about the same season year after year.

#### DIAGNOSIS

When tropical ulcers presenting the typical picture—circular sloughing ulcers with a firm raised edge mostly below the knee—are seen as

ulcer is encountered in other circumstances from other causes and finally resort

to bacteriological examination

Other conditions that have to be excluded are varicose ulcers (not common in the class of patient who is likely to suffer from tropical ulcer), syphilitic ulcers (which can be excluded by a negative Wassermann reaction), yaws (which can also be excluded by a negative Wassermann reaction and by failure to find *Treponema pertenue* in smears from the ulcer), oriental sore (which has a very different geographical distribution and is confined to drier climates, and will show the round forms of *Leishmania tropica* in material taken from the edges of the ulcers, see p 185), and veldt sore.

If a smear is made from the exudate, or better still from a scraping from the base of the ulcer, the characteristic fusiform bacilli, with or without spirochætes will be recognized easily. In a Giemsa-stained specimen, the characteristic beading of the fusiform bacilli will be clearly seen.

#### PREVENTION

As there is still some uncertainty about the cause of *ulcus tropicum*, measures to prevent it cannot yet be placed on a proper scientific basis, but, if meanwhile we adopt certain premises, it will be possible to map

out a provisional preventive programme. These premises are that the ulcers are most likely to occur in people who are ill-nourished and/or debilitated from diseases such as malaria and dysentery, that the causal organism—which is apparently a fusiform anaerobic bacillus—in nature lives as a saprophyte, probably in the soil, and that an epidermal lesion, due to trauma, dermatitis, water sores, insect or leech bite, or to some other cause, is essential for the specific organism or organisms to gain entry. Preventive measures should therefore include, (a) improvement of the diet and general state of health of the population, (b) the protection of the limbs against direct contact with the soil or mud and the early cleansing of the skin thus contaminated, (c) protection of the legs from trauma, contact with irritant plants, and insect and leech bites, and the prevention of hookworm infection and of dermatitis from any cause.

How these recommendations are to be put into practice will depend so much on local conditions that detailed discussion here is out of the question. Very careful consideration should, however, be given before any recommendation is adopted to the most promising theoretical recommendations. The point can possibly be best made on a *priori* grounds.

(i) *Recommendation.* That a shallow concrete reservoir containing antiseptic lotion 18 inches deep be placed so that bare-footed tea garden coolies returning from work have to walk through the tank and cleanse their legs.

*Result.* If the antiseptic was weak & hygienic & the feet were not dried

mental

(ii) *Recommendation.* That tea-estate coolies should be provided with putties to protect their legs from scratches which they are very liable to get from the pruned tea bushes.

*Result.* Very early in the day the putties became saturated with rain and mud, and the wearing of damp puttees for the rest of the day caused dermatitis.

It is possible that in certain circumstances both these recommendations might have been successful, but in most cases they were a failure, apparently for the reasons given above.

The encouragement and if necessary supervision of individual cleansing of the feet of coolies on return from work, and the early treatment of all skin lesions may necessitate the temporary employment of considerable extra personnel on a tea-estate, but may be well worth undertaking if the efficiency of the labour force is seriously threatened at a time of year when most labour is needed, as often happens when there is a serious outbreak.

## TREATMENT

There is no short cut to the successful treatment of this condition, as is evident by the multiplicity and the variety of the methods advocated. Nearly every writer on the subject has some special treatment that he considers the best. In view of the possibility that the name 'ulcus tropicum' is used to describe an aetiological heterogeneous group of ulcers, short accounts of some of the treatments advocated by reliable observers will be included.

### Some Treatments Advocated

'Specifics'.—Parenteral arsenicals, arsphenamine, neoarsphenamine and novarsenobenzol, can claim the largest number of advocates. Various bismuth preparations have also been used with apparent success.

Sodium iodide given by mouth in doses up to the point of producing iodism, combined with local applications of hydrogen peroxide, has had some success. For sulphamidamide and sulphathiazole, good results have been claimed by some workers, and denied by others.

A number of workers have advocated autogenous and specific stock vaccines prepared by various methods, but others consider that equally good results are obtained by non-specific vaccines, and yet others have recommended milk injections.

Under this heading also, the specific action of calcium and of several vitamins, that have been claimed by some—usually isolated—workers should be mentioned.

**Local applications.**—Neoarsphenamine and other arsenicals and sulphamidamide and sulphathiazole have been recommended as local applications. A saturated solution of potassium permanganate (5 per cent) applied by means of a shaped piece of soaked lint to the ulcerated area, only for as long as the patient can stand it, pure phenol or powdered copper sulphate in glycerine (one part in two) similarly applied, crude tar, and powdered cinchona tannin, have each been advocated. More recently, whole blood, serum, and powdered dry plasma have been suggested as dressings. Some success has been claimed for cod-liver oil dressings.

For bathing the ulcers acriflavine, 1 in 1000, potassium permanganate, 1 in 4000, and electrolytic chlorogen have been advocated. Innumerable creams, ointments and dusting powders, in the preparation of which zinc oxide, several bismuth salts, iodine, iodiform, and/or sodium hypochlorite, are combined with olive oil, paraffin or lanolin or boric acid have been suggested.

Surgical procedures, from débridement to total excision of the ulcer, have been proposed.

### PRACTICAL CONSIDERATIONS

In considering the treatment of this condition, it is very necessary to keep the practical aspects of the problem before one. There will, of course, be other circumstances, but a common one will be that in which a large number of coolies in a labour force are suffering from these ulcers and the immediate requirement is to get them on to their feet again in the shortest time possible. In most cases it will pay in the long run to put the patient into hospital (and there will usually be some sort of hospital, however primitive) and treat him thoroughly, rather than to apply palliative measures.

The patient must be kept lying down as much as possible. The wound must be thoroughly cleansed, first with hot magnesium sulphate fomentations, then preferably with hydrogen peroxide, and finally with some anti-

The ulcer itself is then very well treated by a mixture of copper sulphate and phenol in glycerine (half an ounce pow-

dered copper sulphate in one ounce of glycerine to which a drachm of phenol is added), this is allowed to act for a few minutes and is then washed off with normal or hypertonic saline, finally, it is dusted over with sulphonamide, covered lightly with a single or a double layer of gauze to keep off dust and flies but to allow as much air and sunlight as possible to get to the ulcer, the latter appears to have a very beneficial effect in some cases. This is repeated for several days until a healthy red healing surface is left. One or two applications of scarlet-red lotion may help the healing process. After a week or ten days, it will often be possible to cover the area with *tulle gras*, or some such dressing, strap the whole limb firmly or even put on a plaster-of paris casing, and allow the patient to go back to work.

In some cases ambulatory treatment along these lines will be possible. In such cases the phenol 'cauterization' should be very thorough and the strapping or ..... a week or more. Some workers claim ..... inding skin only, putting on a piece of ..... upping or plaster immediately.

Older ulcers with thick fibrous edges will require surgical scraping. This should be done under an anaesthetic and should be thorough, it will also be advisable to swab the ulcer with phenol to complete the operation.

If the area is extensive, skin grafting will be necessary.

During his stay in hospital the patient should be given a good balanced diet, with a full quota of protein and additional vitamins if there are any other indications of specific deficiency.

In cases in which the presence of the Klebs Loeffler bacillus is established specific treatment as for veldt sore should also be given (*vide infra*).

### PROGNOSIS

Left untreated a certain percentage of ulcers will heal in a month or so, but the majority will continue for several months, even up to a year or more.

Under active treatment early ulcers should keep the patient away from work for a few days only, more advanced ones for two to three weeks, and very advanced ulcers for two to three months. A few obstinate cases will be encountered that will lead to the loss of a limb and death may follow septic complications.

### VELDT SORE

**Definition**—Veldt sore is a shallow ulcer appearing on exposed parts of the body that affects white persons, mainly, in hot desert areas, the Klebs-Loeffler bacillus is recoverable from the lesion in a large percentage of cases.

**Discussion**  
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medical men  
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At the time of the Barcoo river flood

... and ... of recent experience

Skin infection with the Klebs-Loeffler bacillus

**Geographical Distribution**—The condition has been reported from a number of localities, mainly in the subtropics where desert conditions prevail, South Australia (Barcoo river), Queensland, North Africa, including Egypt, and the Sudan, South Africa, Gallipoli, Arabia and Iraq, and northern India

### EPIDEMIOLOGY

The disease is largely confined to sojourners in hot desert areas, *e.g.* Australians in the Barcoo rivers area, it was prevalent amongst British soldiers in South Africa in 1899-1901, amongst the colonial and British troops in Gallipoli, Egypt, and Iraq in 1914-1918, and recently amongst the soldiers of the United Nations in North Africa

It is more common amongst fair-haired than dark-haired, and commonest amongst red-haired individuals, it does apparently occur amongst the fairer-skinned natives of the endemic areas, *e.g.* the Arabs of Iraq, but is not common amongst these and is even rarer amongst darker-skinned Africans and Indians

### ÆTIOLOGY

**Historical**—Walshe (1918) noted the association of these sores with diphtheritic paralysis and Craig (1919) demonstrated the presence of Klebs-Loeffler bacilli in the ulcers

Klebs-Loeffler bacilli, *Corynebacterium diphtheriæ*, are recoverable from the well-established ulcer in a large majority of cases. In the pre-ulcerative (vesicular) stage, it is not usually found. This suggests that the lesion in its early stages has some independent cause and that the diphtheria bacillus is superimposed and gives the ulcer its special character, particularly its chronicity

### PATHOLOGY AND SYMPTOMATOLOGY

The lesions usually appear on exposed and hairy parts of the body (although not usually on the head) on the dorsa of the feet, on the knees, on the backs of the hand, on the forearms, and on face, neck, and ears

enlarges into  
first the base  
the infiltra-  
tion sloughs  
to two inches  
slightly in-

durated and the base of the ulcer which is still shallow is covered with a greyish slough the surrounding skin is cyanosed rather than inflamed and there is not usually much exudate. The lymphatic involvement is not constant and probably depends on the nature of the secondary invading organisms.

The special character of the lesions is their obstinate chronicity and their failure to respond to any of the usual treatments for septic sores. They may heal temporarily with a thin epithelial covering which is likely to break down and even when they finally heal they leave a depressed scar that may persist for years.

From the outset the lesion is a painful one at first the sensation is that of pricking and itching then burning and finally there is a frank pain. There are usually some constitutional symptoms fever, headache and malaise.

Very common symptomatic associations with these ulcers which in one reported case

noticed in the limb  
paræsthesia of the  
coordination and a  
encountered or if the sore is on the upper limb loss of power of grip  
loss of tactile sensation and inability to execute any fine movements of  
the hand. Later the toxin reaches the circulation and more distant groups  
of muscles are affected such as the muscles of visual accommodation and  
of the palate.

The nervous symptoms do not usually develop for some weeks after the ulcers first appear and in fact it is often several weeks after the ulcers have healed before the eye symptoms develop.

#### DIAGNOSIS

This is made on clinical and epidemiological on bacteriological grounds or on both.

The investigator must first decide for himself what in his opinion constitutes a veldt sore. He may decide to accept the clinical picture and

or Burma and starting perhaps as leech bites which give an culture of *C. diphtheria*.

The writer feels that the first attitude is the correct one to present. Veldt sore was a clinical entity for many years then Loeffler bacillus was associated with it. The Klebs Loeffler



been shown to be promiscuous in its associations. It does not seem logical to the writer that this bacillus should be allowed to take the name into the humid jungles of Assam and Burma.

A bacteriological diagnosis is made by direct smears (stained with Loeffler's methylene blue), cultures, fermentation reactions and animal inoculations (to determine the virulence).

#### PREVENTION

The initial sores can to some extent be prevented by giving exposed persons protection from the sun, by suitable clothing and protecting ointments (see p. 45), and from the irritating effects of sand and other trauma also by clothing and by frequent bathing, and, in view of the possible effect of diet, one must add, by the giving of a balanced diet rich in vitamins.

The superimposition of the diphtheritic infection can be prevented by early treatment and the protection of all sores and abrasions, and in the case of troops or other communities, by the discovery and suitable treatment of all diphtheria carriers.

A person with infected ulcers should also be isolated to prevent the spreading of infection. It is possible for a patient to develop a faecal infection from his own ulcer, as well as *vice versa*.

Protection of the community by diphtheria toxoid may be indicated in special circumstances.

#### TREATMENT

The treatment of the early sores need not be discussed here, however, when the Klebs-Loeffler bacillus is implanted in the wound, anti-diphtheritic serum becomes a specific. The serum is applied directly to the wound and about 20 000 units given intramuscularly, with the usual precautions. In some instances the effect on the local lesion appears to be dramatic but anti-serum is in any case necessary, in order to obviate or control the neuritic sequelæ.

Topical applications of penicillin (250 Oxford units per c cm) has recently been used with success.

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# LYMPHOPATHIA VENEREUM

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**Definition**—Lymphopathia venereum (*syn* lymphogranuloma inguinale and paradenitis) is a disease of venereal origin, caused by a filtrable virus which produces at the point of entry a primary sore that is frequently overlooked, infection of the inguinal glands in men and the pelvic glands in women, and a series of conditions that have in the past been known severally as 'climatic bubo', 'esthiomene' or ulcer and elephantiasis of the genitals', 'genito recto-anal syndrome' and inflammatory stricture of the rectum.

**Historical**—Climatic bubo has for many years been recognised as a venereal condition common amongst and apparently peculiar to sailors who have visited oriental and other tropical ports. It was thus named by Godding in 1896. Materially the same condition but one with a slightly wider incidence was later described by Durand Nicolas & Favre (1913) and the condition became known in France as

Nicolas-Favre disease. The troublesome chronic ulceration and elephantiasis of the female pudenda sometimes associated with rectal stricture and proctitis has been known to gynecologists for nearly a hundred years (Huguier 1849).

### EPIDEMIOLOGY

**Geographical distribution**—It has a world wide distribution but it is undoubtedly much more common in tropical countries, this is probably less a matter of climate than of social conditions (*vide infra*).

**Social, sex and race distribution**—It is a venereal disease. It is particularly associated with the low class prostitutes that frequent dock areas in most countries in the world. The disease is very prevalent in Mediterranean, South American and Eastern ports, where such prostitutes abound and where little or no control is exercised over them.

In a woman evidence of the disease will often be concealed so that she may be unconscious of the infection and transmit it to a number of men, men are therefore more frequently affected. Further, for the same reason men will be more likely to seek medical advice and the sex disparity will be exaggerated.

cent of the outpatient population. Further, Kreis test surveys indicate that a high percentage of the negro patients at venereal clinics suffer from this infection without necessarily showing any symptoms.

### ETIOLOGY

**Historical**—In 1924 Gamna described certain chromatin-staining bodies as the cause of lymphogranuloma inguinale in Japan. In 1925, in Japan, the disease was called "lymphogranuloma inguinale" and "granuloma inguinale".

actually the virus

The causal organism is a filtrable virus between 0.127 micron and 0.175 micron in diameter, it passes through Seitz E and K, Chamberland 1, 2 and 3 and Berkefeld V and N filters. It is transmissible to most laboratory animals except rats. Mice are the most suitable experimental animals in these animals an encephalitis is produced and from the brains of infected mice antigen has been prepared for Frei's test. It grows on the yolk sacs of developing chick embryos and from this source also an antigen has been prepared.

### PATHOLOGY

The virus gains entry through a small abrasion in the skin or mucous membrane or possibly through the intact epithelium, usually of the prepuce or glans penis in men and of the vagina or the cervix in women but in

the latter the primary sore may be on or near the clitoris, in the fourchette or on the labia. Primary lesions around the anus and on the lips have been attributed to unnatural practices. Extra genital primary lesions have also occurred in children, the infection having been transmitted by contact with bed companions.

There is little local reaction. The epidermis becomes slightly thickened, but there is no downgrowth into the papillary layer. There is no granulomatous reaction, but some infiltration of plasma cells, lymphocytes, and polymorphonuclears, and some exudation which raises the superficial layers and produces a nodule, a papule, or just vesiculation. The papules break down or the vesicles burst leaving a shallow abrasion which may be surrounded by a narrow band of hyperæmia but little infiltration.

Thence the virus passes along the lymphatics to reach the first group of lymph nodes. In the case of men, this will be the inguinal glands, this will also be the case in women in whom the primary sore was in the anterior part of the vulva, but this is rare as the lesion is more often in the vagina, and from here the infection is carried to the lymphatics in the wall of the anal canal and lower end of the rectum, and then by reflux infection to the deep pelvic glands, which include the peri-rectal and retro-peritoneal. The wall of the lower end of the rectum and anal canal becomes thickened and later contracts causing a stricture.

In the glands, pin-point epithelioid formations, with giant cells and large reticulo-endothelial cells appear. The centres become necrotic and

form. Around the gland there is a plastic peri-adenitis. Several of these stellate necrotic areas coalesce and form an abscess, which then becomes secondarily infected and suppurates, or it may dry up and become partly absorbed, but fibrotic changes occur in the surrounding tissue, and scars form and eventually contract.

Suppuration is usually the fate of the superficial, inguinal glands, the pus tracks to the surface leaving a number of sinuses which are further infected and become chronic. However the deep pelvic and peri-rectal glands seldom suppurate, but during the healing process there is a considerable amount of fibrotic contracture which may cause a stricture of the rectum at a higher level than that referred to above.

vide), so that the final state is often one of chronic ulceration.

There are thus four stages in the pathogenesis of this infection, namely,

- (i) the symptomless stage of invasion,
- (ii) the primary lesion,
- (iii) the invasion of the lymphatic glands, and

(iv) the sequelæ, due to the fibrotic changes in or around the glands, causing rectal stricture and/or lymphatic obstruction with elephantiasis and ulceration.

**The Blood**—There is no characteristic blood picture, but in the majority of cases there is a moderate leucocytosis with a relative large mononuclear increase, later, there may be a normal white-cell count with a slight relative lymphocytosis.

There is an increase in the sedimentation rate, and a marked lowering, or even an inversion, of the albumin/globulin ratio, to the extent of causing a positive aldehyde test (see p 164) in rare cases.

### SYMPTOMATOLOGY

The symptomatology can best be considered under four headings corresponding to the four stages in pathogenesis enumerated above.

(i) **Incubation period**—From the time of exposure to infection to the first appearance of the primary sore is only a few days, but if this is missed it may be a month or more before the other lesions reach the clinical stage.

(ii) **The primary sore**—This commences in the localities noted above as a vesicle or cluster of vesicles which burst and leave a small shallow ulcer with a white or greyish base and clean cut edges surrounded by a narrow band of slightly reddened skin which is not indurated, it is usually painless, it heals rapidly, and it leaves no scar.

In some areas, it may be possible to trace the lymphatic spread by feeling a cord like lymphatic vessel, *e.g.* along the wall of the vagina and in these cases nodules may form along the course of the lymphatic vessel and may later break down.

(iii) **The secondary phase**—The onset of this phase is usually from two to six weeks after the initial infection and often occurs with marked constitutional symptoms, fever, headache, arthralgia and malaise. The fever which may be high does not follow any specific pattern, and may be mistaken for that of typhoid plague, or other febrile disease, it may fall when the buboes develop, or continue and eventually become a septic type of fever as the buboes suppurate. Rashes and skin eruptions, eye changes and other symptoms suggestive of an allergic reaction may occur.

The buboes which are frequently bilateral, are at first soft and rubbery, discrete and slightly tender, later, they become matted, adherent to the underlying tissues and to the skin and very tender. If they are felt carefully, soft fluctuating points will be identified. They may heal spontaneously leaving a dimple where the skin has been caught in the retracting scar tissue, but, as indicated above, the inguinal glands usually become secondarily infected suppurate and, if they are not opened discharge through one or more sinuses. Sometimes further secondary infection causes sloughing of the skin and an open ulcer is formed which is usually very chronic. The iliac glands may be affected and although these are much less likely to suppurate, it is often possible to feel the large mass of enlarged glands in the iliac region.

In women when the pelvic glands are infected there will often be no localizing signs accompanying the febrile attack to indicate its nature except possibly a heaviness in the pelvis, some low back pain, and dyspareunia.

(iv) **The tertiary phase**—There will be an interval of several months to several years before the next phase becomes established. The symptoms

of rectal stricture are usually frank dysentery (i.e. the passage of blood and mucus) or alternate diarrhoea and constipation as in carcinoma recti. The stricture can be seen through the sigmoidoscope with an inch or so of ulcerated and sometimes necrotic mucous membrane below and there is almost certainly (although it cannot be seen) several inches of ulcerated bowel above the stricture to account for the blood pus and mucus coming through the stricture opening and for the associated pain and tenderness

anus. Ulcers develop and spread involving all the soft parts which break until eventually high urine and early of certain even years but exhaustion

### DIAGNOSIS

The clinical diagnosis in the well-developed and typical case should not present any difficulty but there will be many cases in which the syndrome is only partially developed and in which a confirmation of the diagnosis will be welcome. The finding of Gamna bodies and the granulo corpuscles in histiocytes in biopsy material will provide some additional evidence but these findings cannot be considered specific. It will therefore be necessary to do Frei's test to obtain absolute confirmation of existent or at least recent infection with the specific virus.

**Frei's test**—There are four sources for the antigenic material for this test namely (a) aspirated pus from an inguinal or other bubo of a diagnosed case\* (b) macerated material from an infected gland (c) mouse brain emulsion from a cerebrally infected mouse\*\* and (d) emulsion of yolk sacs inoculated with the virus. The first is probably the most satisfactory but it is very difficult to obtain uncontaminated pus in sufficient quantities and for this reason the mouse brain antigen came into general use some years ago. It is acknowledged that this gives less clear cut results and that it is necessary to measure the papules carefully and to compare them with a normal mouse brain control to ensure a satisfactory result (Grace and Sulkin 1936). Sulkin (1941) using a yolk sac antigen prepared by Rake, McKee and Shaffer (1940) reported more specific results than he obtained with mouse brain antigen. A complement fixation test can be done with this same antigenic material this gives a very specific result.

The test becomes positive within 14 days of the first appearance of the primary lesion in a very large majority of cases rarely the positive reaction is delayed for another week. It usually remains positive a long

\* To prepare this antigen pus must be obtained by aspiration from an unopened bubo in a patient who has no other venereal disease. This is diluted with four parts of saline, heated to 60°C for half-an-hour on three consecutive days and tested for sterility by aerobic and anaerobic technique. If possible its antigenic properties are tested on a known case of the disease after which it is ready for immediate use but can be kept for some time in the cold. A more satisfactory method of preserving the antigen is to freeze the pus and dry it in vacuo; the powdered pus is dissolved in 50 parts of normal saline when it is required for use.

\*\* Commercial preparations are available.

as there are lesions and often for some time after they have healed. The test is positive in about 90 per cent of cases of chronic ulcerative elephantiasis of virus origin.

It has been shown that both the intradermal and the complement fixation tests remain positive as long as the virus is present, and, conversely, if the reactions are positive, it is evidence that the virus is still present. This may be as long as 25 years after infection, and it is possible that such persons are still infectious.

**Technique**—An intracutaneous injection of 0.1 c. cm. of antigen is given into the skin of the arm or leg and at the same time an injection of similar substance that does not contain the specific antigen is given a few inches away. The result is read after 48 hours.

**The result**—With Frei's pus antigen, a papule of at least 5 mm. in diameter and with either the mouse-brain or the yolk-sac antigen of at least 7 mm. constituted by a hyperemic halo and some

The extreme limit of a non-specific reaction is of the order of 1 to 4 mm. in diameter.

**Precaution**—Frei (1938) recommends that the test should not be done in the 'peracute' stage or in cases where there is suppuration near the perineum on account of the dangers of a generalized or local reaction.

This disease may be a diagnosis of some importance to exclude the possibility of venereal diseases having been established. Frei's test is used in venereal clinics.

when taken also gives a reaction.

**Differential diagnosis**—The buboes must be distinguished from other glandular swellings, acute enlargement, e.g. sepsis, chancre, glandular fever, plague, tularemia, and malignancy, the elephantiasis and ulceration from filariasis and other causes of lymphatic obstruction, from granuloma venereum, chancre, cancer, tuberculosis, and actinomycosis, and the rectal stricture from cancer, syphilis, tuberculosis, ulcerative colitis, and other dysenteries.

## PREVENTION

Under this heading it is only possible to make very general remarks. In this connection pathia venereum is, for example, obviously preventable by the observation of the simple rules of hygiene. Secondly, although, as stated, there is every reason to believe that it is a disease associated with poverty and a lack of hygienic knowledge, its prevalence is not yet fully known, nor whether persons with sub-clinical infections act as carriers. Thirdly, it has not received the attention of medical schools it deserves, not even in special classes on venereal diseases. Lastly, there is as yet no treatment that can be considered a true specific for the disease.

reporting of the clinically obvious cases of this disease imperative, but clinically obscure cases must be sought out, Frei's-test surveys should be

carried out in certain populations, *e.g.* amongst prostitutes, and should be adopted as a routine practice in venereal clinics. As satisfactory antigen is now obtainable commercially, this should not present any great difficulty.

Much can now be done by early recognition and treatment of the disease to limit its spread, but if a true specific could be found this line of attack would obviously be considerably facilitated.

### TREATMENT

In view of the diversity of the lesions it is obvious that any adequate discussion on treatment would lead one far beyond the scope of this book so that it will be necessary to confine remarks mainly to medical treatment.

No true specific treatment has yet been found. Some promising early reports on the use of certain 'sulpha' drugs were published, but none of these drugs has lived up to this early promise which is not surprising in view of their total lack of success in other virus infections.

There is evidence that in the early stages antimony will sometimes cut short the infection. The drugs used have been sodium antimony tartrate and Fouadin or its chemical equivalents for dosage see *GRANULOMA VENEREUM*. Gold preparations have also been used but as their administration is not without danger and as their specific action in this disease is uncertain it seems unjustifiable to use them.

6 grammes daily) continued for several weeks improvement appears to be effected in a certain number of cases. The reversal of a positive Frei's test is evidence of cure.

In rectal stricture considerable improvement in the secondary bowel condition is effected by placing the patient on sulphanilamide three grammes daily for twelve days alone or combined with 3 per cent. sulpha drug bowel washes. When the inflammatory condition subsides the stricture disappears and it is often possible to avoid any surgical interference.

The treatment by increasing doses of Frei's antigen that was advocated at one time was not a great success and has been largely abandoned.

Buboes should be treated by local applications of heat, infra red rays or hot fomentations and later when they become soft and fluctuating they should be aspirated with a sterile syringe and sealed rather than opened and drained.

### PROGNOSIS

Despite the absence of a truly specific treatment if treatment is undertaken early, the prognosis appears to be good. This is especially true in the case of men. In uncomplicated rectal stricture when the pelvic adnexa are not involved to any extent even when medical treatment has failed something can usually be done surgically. In cases in which lymphatic obstruction is already established great care which may be difficult or impossible to maintain, is necessary to prevent ulceration. Finally when there is extensive ulceration with fistulae already formed the condition is hopeless as the unhealthy tissues will not stand up to any plastic operations.







**Generalized form.**—Recently, a most unusual case in which there were lesions on all parts of the body was seen in New Orleans. Some of the lesions, on the back for example, seemed to preclude direct or indirect external transfer of infection, and suggested dissemination of infection via the blood stream.

To summarize, there may or may not be a primary shallow ulcer,

### DIAGNOSIS

An early diagnosis is very important as treatment in the early stages is much easier and is more effective. A clinical diagnosis can be made with a fair degree of certainty in many cases, by the nature of the bright red velvety lesions which bleed easily and in the early stages are button-like, however, whenever possible the diagnosis should be confirmed by the finding of the specific Donovan bodies in smears from the exudate, from scrapings recovered from the bases or sides of the ulcers, or in biopsy material. This will be easier in the early stages of the infection, as in the late stages the specific organisms become very scanty.

The smear should be stained with Wright's, Leishman's or Giemsa's stain.

The 'Donovan body' has to be distinguished from the round form of leishmania, to which it bears only a very superficial resemblance (see p 143), from histoplasma, from the pneumococcus, which is gram-positive, from the gonococcus, and from Friedlander's bacillus, which also being gram-negative and having a well-developed capsule will present the only real difficulty.

If there is any doubt, a culture on an ordinary agar slant should be made, on this, Friedlander's bacillus will grow, but not, of course, the 'Donovan body'.

A stain which will differentiate the Donovan body from 'other' bacteria, especially of the Klebsiella group, has been suggested by Mortara and Dienst (1943).

**Technique.**—Make a smear and dry it rapidly in the air or by gentle heat. Stain for two minutes with basic fuchsin (0.5 per cent aqueous solution). Decolorize in 0.5 citric acid solution for approximately five seconds and counter-stain with 1 per cent aniline blue.

**Result.**—This will stain the intra cellular Donovan bodies a pink colour and the so called capsule a light blue, bacteria will mostly take the blue stain.

Further confirmation can be obtained from the ready response of these lesions to suitable antimony treatment (*vide infra*).

**Differential diagnosis.**—The condition will have to be differentiated from chancroid (soft sore or Ducrey's infection) by the absence of the characteristic soft glandular dermal melanos antigen, of the early lesion, and its enlargement, (ii) a positive antisyphilitic treatment, absence of glandular enlargement and tuberculous

and carcinomatous ulceration—by the absence of the characteristic histological pictures in the biopsy material

### PREVENTION

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In the  
a symp-  
tomless carrier state can exist, as is suspected in the former disease, and, secondly, trivalent antimony acts as a specific

### TREATMENT

This should be considered under three headings —(i) local, (ii) specific, and (iii) surgical

(i) **Local treatment**—If there is acute inflammation hot magnesium sulphate fomentations should be applied until this subsides. The lesions

this application prove too painful, it may be preceded by the application of some anæsthetic ointment (e.g. pantocaine 4 per cent or anæsthesin), which allows it to act for ten minutes before the podophyllin is

As an alternative to podophyllin, four per cent potassium antimony tartrate (tartar emetic) is used, as before after the preliminary application of some anæsthetic ointment

This local treatment may be applied without any specific treatment, but more rapid cure will be effected if the local and the specific treatment are combined

(ii) **Specific treatment**—Antimony preparations have proven the most successful. Many have been advocated but the most successful have been the simple potassium and sodium antimonyl tartrates and the more complex foudadin (pyro-catechin sodium bisulphonate *HP* stibophen). More recently, anthiomaline (lithium antimony thiomalate) has been used with limited success (Robinson and Robinson, 1942)

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be commenced after two to three weeks interval or one of the other antimony preparations may be substituted. It is important to continue the treatment for some time after the lesions have healed as they are otherwise liable to relapse

The course and dosage with either sodium or potassium antimonyl tartrate is the same as that given in kala-azar (see p 163). Anthiomaline is

given in 2 cc doses of a 6 per cent solution, from 12 to 15 doses usually being necessary

(iii) **Surgical treatment**—Complete excision of the primary sore and the early secondary lesions is often possible, and should always be considered when an early diagnosis has been made, but partial removal of a large lesion usually leads to infection of the wounds and extension of the process

Again, in the later stages after the specific organism has been destroyed as a result of the specific treatment, there will often be a large

the perineum have been destroyed or contractures have taken place plastic surgery will have to be considered

### PROGNOSIS

The earlier the treatment is undertaken the better are the chances of a rapid cure. With suitable specific treatment the prospects are excellent in early cases and, even in the more extensive ones, provided there are no serious complications and the patient will cooperate, cure and repair should eventually for many the life of

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given in 2 c cm doses of a 6 per cent solution, from 12 to 15 doses usually being necessary

(iii) **Surgical treatment.**—Complete excision of the primary sore, or the early secondary lesions is often possible, and should always be considered when an early diagnosis has been made, but partial removal of a large lesion usually leads to infection of the wounds and extension of the process

Again, in the later stages, after the specific organism has been destroyed as a result of the specific treatment, there will often be a large raw surface left and it may be necessary to scrape or trim the fibrotic edges before the epithelium will begin to grow in from the margins, and, if the

### PROGNOSIS

The earlier the treatment is undertaken the better are the chances of a rapid cure. With suitable specific treatment the prospects are excellent in early cases and even in the more extensive ones provided there are no

the life of the patient

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**Introduction**—There are few true\* skin diseases that are confined entirely to the tropics but several are undoubtedly more common more severe and acquire a special significance in tropical climates. It is to some of the more important of these that this chapter is devoted. Every white sojourner in the tropics will know prickly heat, dhobie itch and ring worm of the feet—by their or some other names—as actual afflictions or ever-present dangers. Pityriasis versicolor which is a widespread infection amongst natives of the tropics and leucoderma which is a common enough condition in the tropics to justify its inclusion here are more important from an æsthetic than from a morbidity point of view but should be recognized as they may well be confused with other more serious conditions. Finally tinea imbricata is perhaps the only skin disease that has an exclusively tropical distribution.

These conditions will be discussed mainly from the clinical point of view.

## PRICKLY HEAT

Prickly heat is probably the commonest of all syndromes suffered by the newly arrived white man in the tropics, and history has recorded that

## EPIDEMIOLOGY

It occurs in all tropical and in many sub-tropical countries but is especially associated with the 'green' tropics and with the periods of year when humidity is high, e.g. the monsoon in India

The dark-skinned native of the tropics rarely suffers from this condition. It is far more common in the newly arrived sojourner than in the older residents, but the white man seldom becomes completely immune

most pronounced in the obese

It was more common in the past when the British soldier in India wore heavy broadcloth, when the sojourner wore the formal dress of his country of origin, and when the cholera belt was considered an essential precaution, than it is today when the dress of both the soldier and the civilian sojourner is more rational. It occurs more commonly amongst those persons whose circumstances prevent regular bathing and changing of clothes

## ÆTIOLOGY AND PATHOLOGY

On the subject of the ætiology of prickly heat, there are several schools of thought

Smith (1927) claimed to have isolated a yeast like fungus, apparently a

The actual cause of the lesions is blocking of the small sweat ducts

Perpetual sweating causes the washing out of the fat from the epidermis, so that these tissues absorb water and become swollen and soft. The less completely cornified skin of infants is more readily affected. This

swelling leads to occlusion of the openings of the ducts, where the blockage is made complete by desquamated diet on the skin. The damage is

poor invasive properties. There is already hyperæmia of the skin and the infection causes a slight inflammatory reaction. Whenever anything occurs to increase the skin hyperæmia, sweat secretion is stimulated and there is tension within the blocked ducts. The hair follicles are also involved but to a less extent.

**Anatomical distribution**—It occurs on parts of the body (a) where the clothes are held in close contact by pressure, e.g. around the waist under the belt on the shoulders where the weight of the clothes is taken and across the shoulder-blades, (b) where there is friction from the clothes, e.g. in the groin, axilla and the backs of the wrists, (c) where two skin surfaces are in continuous contact, e.g. under the breasts and between the folds of fat in the obese, and (d) on the backs of the hands, a site where the frequent presence of prickly heat cannot be explained on any of the above grounds.

### SYMPTOMATOLOGY

The lesion consists of red papules and minute clear vesicles with a surrounding red halo, or sometimes on a general hyperæmic background which gives the skin a red granular appearance and a rough, coarse-sand paper-like texture. A white powdery desquamation occurs later.

Anything that will cause a hyperæmia of the skin, such as exercise or a hot bath or a cup of hot tea, will cause an immediate exacerbation of the symptoms, a prickling sensation and intolerable itching.

The extremely irritating nature of the lesions causes scratching which will often lead to deeper secondary infection with pyogenic micro organisms and may result in the development of folliculitis, eczema and/or furunculosis.

Bromfield (*loc. cit.*) described the miliarial (as above), the pustular, the pemphigous and the impetigenous types of prickly heat, but it seems more satisfactory to consider these other types, together with multiple boils which he includes as a fifth type, as complications, for in the ordinary circumstances in which prickly heat is common they are relatively rare, further, they have causes other than prickly heat though it may be a common one.

Ordinarily, prickly heat is a minor annoyance to the resident in the tropics but it may dominate the mind of the sufferer, interfere seriously with his sleep and lead him towards neurasthenia, it is more serious in children as not only will it disturb their sleep, but the common complications are more likely to develop in their delicate skins, and in the sick, though it may be easy to control, if neglected prickly heat will often be a serious complicating factor in their illness.

### PREVENTION AND TREATMENT

It is very much easier to prevent than to cure this condition.

The aims of prevention are the avoidance of the conditions (*vide supra*) that favour and precipitate the condition—



swelling leads to occlusion of the openings of the ducts, where the blockage is made complete by desquamated duct epithelium. The damp surface provides a suitable nidus for micro-organisms of all kinds and the damaged sweat ducts soon become infected with the common skin-inhabiting micro-organisms, including monilia, which are mostly of low virulence and have poor invasive properties. There is already hyperæmia of the skin and the infection causes a slight inflammatory reaction. Whenever anything occurs to increase the skin hyperæmia, sweat secretion is stimulated and there is tension within the blocked ducts. The hair follicles are also involved but to a less extent.

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### PREVENTION AND TREATMENT

It is very much easier to prevent than to cure this condition.

The aims of prevention are the avoidance of the conditions (*vide supra*) that favour and precipitate the condition—

- a) Avoiding as much as possible the environmental conditions namely high temperature and humidity that produce prickly heat much can be done by the use of air conditioning and the electric fan
- b) Avoiding unnecessary exertion unless the immediate removal and change of clothing is possible
- c) Avoiding hot baths unless ample time can be allowed for cooling off before redressing
- d) Avoiding the taking of long draughts especially of warm tea or coffee when fully dressed
- e) Reducing clothing to a minimum and avoiding constrictions around the waist neck wrists etc Children should be allowed to be naked or at most wear a pair of pants and infants should be spared from wearing even a diaper
  - o the skin and change
  - The removed under
  - mediately with anti
- g) Bathing and/or taking a shower bath with tepid water at least twice a day
- h) Avoiding the too free use of ordinary soap in the bath but washing over with special antiseptic soaps and leaving the lather on to dry with the precaution that sensitivity to such soaps must be carefully tested by each individual
- i) Drying the body thoroughly cooling off under an electric fan and finally before putting on the clothes dusting the whole body (except sensitive spots) and especially those areas most liable to prickly heat with an antiseptic dusting powder
- j) At night in the absence of air conditioning or an electric fan using a hard mattress with a sheet of grass matting between it and the under sheet a firm pillow and a Dutch wife that is a hard bolster or an open rattan work cylinder over which the legs and arms can be thrown to keep them apart and from lying against the body
- k) Keeping a supply of hand towels for mopping the face arms and other exposed parts of the body repeatedly these must be washed and dried frequently

It may be considered that much of this is counsel of perfection but it is by following these practices that many experienced sojourners avoid prickly heat altogether The less fortunately placed must adopt as many of these practices as possible

In addition to the above judicious sun bathing is to be recommended as the tanned skin is not so liable to prickly heat This is particularly true of infants and children

Some observers consider that a reduction of the fat and carbohydrate in the diet with an increase of the protein is of value in reducing liability to prickly heat but the only dietary modification from which the writer has seen direct benefit is the addition of extra salt (2 gramme tablets to each pint of water) This is an important point which should be emphasized The taking of a balanced diet with all the vitamins will of course help to maintain good health and indirectly reduce both prickly heat and more particularly its complications

The aims of treatment are much the same as those of prevention. It will however usually be necessary to adopt more aggressive tactics.

All, or as many as possible of, the above precautions should be observed rigidly. After the bath the affected parts must be lathered with antiseptic soap which should be allowed to dry on the skin. The tolerance of each person to each soap must be ascertained. Some sensitive individuals will be 'burnt' if 'neko' soap, for example, is left on for more than two minutes, so that after this interval it must be sponged off, 15 minutes is usually the time recommended, but in the case of the less sensitive it is unnecessary to wash off the soap at all. 'Asepto', 'Afridol' and 'neko' soap are to be recommended. The two former being the better.

As an alternative to the antiseptic soap and to be applied at other times is a lotion of 1 in 2000 perchloride of mercury in 95% alcohol to be wiped over the affected part after it has been dried, and itself allowed to dry. (This will not suit all skins.) Then a dusting powder, consisting of camphor—20 parts, menthol—5 parts, boric acid—200 parts, zinc oxide—300 parts made up to 1000 parts with fine talcum powder, should be applied.

As an alternative to the mercury spirit lotion and powder, a white lotion made up of zinc oxide 20 per cent, menthol 1 per cent, camphor 2 per cent in 80 per cent alcohol should be dabbed on the affected area with a piece of cotton wool. It is usually inadvisable to apply this more than twice during the day. At other times an aqueous calamine lotion with phenol will be soothing.

As in the case of most skin disease, there is greater danger from over-treatment than from under-treatment, and whenever any treatment appears to be irritating the skin, it must be discontinued and simple aqueous calamine lotion applied.

The sulphonamides have no effect on uncomplicated prickly heat, but, for the complications in which pyogenic organisms play a part, sulphathiazole and sulphadiazine will be of considerable value.

#### PROGNOSIS

### RINGWORM OF THE FEET (TINEA PEDIS) OR DERMATOPHYTOSIS

This is a worldwide condition but always assumes a much greater importance in the tropics and particularly in the humid tropics. In temperate climates, where it is usually known as 'athlete's foot', it often appears in epidemic form in schools and amongst athletic groups whose members transmit the infection to one another in dormitories, changing-rooms and swimming baths, by walking barefooted and by the communal use of bath slippers, sandals and towels. In the tropics, where it has innumerable synonyms, *e.g.*, Hong Kong, Singapore, Bengal, etc., foot-rot (indicating its geographic distribution), mangoe toe, etc., it is endemic.

and, where there are native servants walking barefooted, it is practically impossible to avoid infection, even by taking the most rigid precautions

### EPIDEMIOLOGY

pavements) than in country districts, amongst men than amongst women, and amongst those who have to do a considerable amount of walking during the day (e.g. brokers) than amongst those whose occupation is mainly sedentary (e.g. bankers). The barefooted are usually infected, but the infection is seldom active, and, in any particular set of circumstances, the activity of the condition will usually be in inverse ratio to the ventilating properties of the footwear.

### ÆTIOLOGY AND PATHOLOGY

The causal organism is a fungus, usually a species of *Trichophyton*, but *Epidermophyton floccosum* and even the monilia, *Candida albicans*, may be responsible, the spores of these fungi are highly resistant and survive on wooden floors, coir or grass mats, carpets, towels, shoes etc., almost indefinitely, despite vigorous treatment with strong antiseptics. They are destroyed by autoclaving.

These fungi penetrate the epidermis and the superficial layers of the corium only and their toxins cause a serous exudate to accumulate under the epidermis which is thus separated from its source of nutrition and dies.

### SYMPTOMATOLOGY

The primary site of the infection is often between the fourth and fifth toes; it soon spreads to the other interdigital spaces, to the soles, to the dorsum of the feet and particularly of the great toe to the sides of the feet, to the soft area of skin between the ankle and the Achilles tendon, and to the nail-beds. The same infection may also spread to other parts of the body (*vide infra*).

Small vesicles appear, they are usually surrounded by a halo of inflammation. They are extremely irritating. Between the toes become white and exposing the red corium covered by a which tends to crack, bleed if damage infected with pyogenic micro organism the epidermis gradually resumes its sodden and separates again. Meanwhile, areas of hyperkeratosis develop at the margins of these lesions and form ridges along the edges of the dorsa of the toes and up the interdigital sulci on to the dorsa of the feet. The infection will usually spread to the soles, especially to the parts under the arch where the skin is thinnest, here the vesicles in the comparatively thicker epidermis pence (¾ in often develop too, the epidermis the denuded cellulitis may result



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### PROGNOSIS

This will depend on the personal factor, on the opportunities for applying the measures recommended, and on the vigour and wisdom with which they are applied. Seldom, if ever, should it be necessary to invalid patients for uncomplicated prickly heat, but when they persistently develop multiple boils a short period of leave in a cool climate often appears to be the only way to cure this serious complication.

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and where there are native servants walking barefooted it is practically impossible to avoid infection even by taking the most rigid precautions

### EPIDEMIOLOGY

This disease is at its worst under conditions of high temperature and

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Small vesicles appear. They are usually surrounded by a halo of inflammation. They are extremely irritating. After a few days the whole areas between the toes become white and pieces of sodden epithelium separate, exposing the red corium covered by a thin transparent layer of epidermis which tends to crack, bleeds if damaged by scratching and readily becomes infected with pyogenic micro-organisms. After such infection has subsided the epidermis gradually resumes its normal thickness but soon becomes

arch where the skin is thinnest. Here the vesicles in the comparatively thicker epidermis cause intolerable itching and develop to the size of a sixpence ( $\frac{3}{4}$  inch) or more. These blebs contain a clear fluid at first but they often develop into pustules surrounded by areas of inflammation. Here too the epidermis may separate in large plaques but it usually flakes off. The denuded skin tends to crack and secondary infection and extensive cellulitis may result.

The aims of treatment are much the same as those of prevention. It will however usually be necessary to adopt more aggressive tactics.

All, or as many as possible of, the above precautions should be observed rigidly. After the bath the affected parts must be lathered with antiseptic soap which should be allowed to dry on the skin. The tolerance of each person to each soap must be ascertained. Some sensitive individuals will be 'burnt' if 'neko' soap, for example, is left on for more than two minutes, so that after this interval it must be sponged off, 15 minutes is usually the time recommended, but in the case of the less sensitive it is unnecessary to wash off the soap at all. 'Asepso', 'Afridol' and 'neko' soap are to be recommended. The two former being the better.

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The socks should be of thin cotton material and must be changed at least twice daily, washed immediately in antiseptic lotion and dried thoroughly before being put on again, and boiled periodically. After the feet have been washed with lotion or antiseptic soap, the interdigital spaces should be dried by rubbing hard between the toes with a rough dry towel to remove all pieces of loose skin swabbed with spirit and finally powdered with some mild antiseptic powder. A useful prescription is

℞ Camphor—2 drachms  
sulphur sublimate—½ ounce  
zinc oxide—2 drachms  
talcum powder—2 ounces

As some individuals are sensitive to sulphur, it may be necessary to omit this from the prescription.

### TREATMENT

The greatest danger is from overtreatment and for this reason many people are content, without attempting to cure the condition to keep it inactive by the measures advocated above.

The patient will usually first come for treatment when the lesions are actually inflamed either as a result of neglect or inexpert overtreatment. It is necessary first to reduce the inflammation by hot (as hot as the patient can bear) footbaths of 1 in 1000 mercury perchloride or acriflavin, or boracic or magnesium sulphate fomentations alternating with calamine absided after careful removal of all gentian violet 4 per cent in 10 per cent and brilliant green 2.5 grammes e)

For complete eradication of the infection the following lotion should be applied twice daily

℞ Salicylic acid—gr xx  
Dilute acetic acid—min xxx  
Alcohol—95 per cent to the ounce

If there is a sharp local lesion this treatment must be stopped immediately and hot fomentations applied.

The socks must be changed twice daily and after a thorough course it will be advisable to discard all old shoes which are almost certainly infected and which cannot be sterilized by any known means.

As the nails and nail beds are often a source of re-infection special attention must be paid to these. They constitute a very difficult problem and often the nail has to be removed and the bed scraped. The possibility of complete failure to cure the nail infection must be faced.

The nails must be treated by hot footbaths and fomentations and true id treatment, castrous workers

Some workers have claimed considerable success in chronic cases with an autogenous vaccine made from the pyogenic secondary invaders which they claim interfere with the action of the fungicidal drugs. The local treatment is continued while the vaccine is being given.

## DIAGNOSIS

## PREVENTION

(a) — " — — — —  
ons ir  
e, but  
nce of infection and the frequency of re-infection, namely—

- (i) By avoiding going barefooted even in ones own bathroom
- (ii) By using a bath mat that can be boiled frequently and avoiding one that cannot be so treated
- (iii) By using rope or canvas-soled bath slippers that can from time to time be placed in boiling water or cheap grass (raffia) sandals that can be discarded periodically
- (iv) When changing outside ones own house by being particularly careful and always using ones own bath mats towels and slippers and avoid bathing pools except those with a very high standard of cleanliness

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hoes should be avoided  
dent' shoes in which the  
orated leather shoes, or  
haplus', the last named is a form of shoe worn by northern Indians and  
ade with two leather flaps which overlap one another and are held in  
ace by a strap and buckle All these types of shoe allow a free circula-  
on of air

The socks should be of thin cotton material and must be changed at least twice daily, washed immediately in antiseptic lotion and dried thoroughly before being put on again and boiled periodically. After the feet have been washed with lotion or antiseptic soap the interdigital spaces should be dried by rubbing hard between the toes with a rough dry towel to remove all pieces of loose skin swabbed with spirit and finally powdered with some mild antiseptic powder. A useful prescription is

R Camphor—2 drachms  
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zinc oxide—2 drachms  
talcum powder—2 ounces

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R Salicylic acid—gr xx  
Dilute acetic acid—min xxx  
Alcohol—95 per cent to the ounce

If there is a sharp local lesion this treatment must be stopped immediately and hot fomentations applied

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The toes must be treated by hot footbaths and fomentations and mild antiseptic lotions. Later the triple dye may be used. In a true 'id' there is no specific mycotic infection at the site and vigorous treatment with strong salicylate preparations for example will usually be disastrous. The mycotic infection at its distant focus however may and some workers consider that it should be treated specifically

an s  
they  
treatment is continued while the vaccine is being given

## DHOBIE ITCH OR TINEA CRURIS

The name is derived from the popular tradition (undoubtedly founded on fact) that the *dhobie*, or Indian washerman before returning to their owner the clothes he has taken home to wash, lends or hires them out to his friends, whose mycotic infections are thus widely disseminated

### EPIDEMIOLOGY

This is an exceedingly common condition amongst both the native inhabitant and the sojourner in all tropical and many sub tropical countries, and though it does occur in temperate climates especially in epidemic form in schools, it is relatively uncommon

It is very common in the middle-class clothes wearing native of the tropics and occurs, though less frequently, even in those who wear only a loin cloth, amongst sojourners it is not uncommon in the newly arrived and amongst members of the lower social strata, however, the better class native and the experienced sojourner will not usually tolerate the condition, but will take active steps to prevent it

It is more common amongst men than women

It is more common in humid climates but it does not appear to be as dependent on high humidity as are prickly heat and tinea pedis

### ETIOLOGY

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ve rise to the  
'ures of these

### SYMPTOMATOLOGY

The two main areas in which this condition develops are, (a) the inner aspects of the thighs where radiating from the crutch it passes backwards to the perineum, on to the scrotum and into the anal cleft and (b) the axillæ where it spreads out on the lateral aspects of the chest and on the under and inner sides of the arms the former site is by far the commoner The condition is usually bilateral

A red rough scaling area with a raised spreading papular and often pustular margin develops the lesion spreads fan wise It is intolerably irritating and thus causes continuous and involuntary scratching even in the sleep which allows secondary infection to occur and increases inflammation The inflammation may be so severe that the patient can scarcely bear to put on his clothes and can walk only with great difficulty

### DIAGNOSIS

This can be confirmed by taking scrapings from the margins of the lesions and macerating them in 20 per cent potassium hydroxide as in the case of tinea pedis

### PREVENTION

This condition is not nearly so difficult to prevent as tinea pedis A good supply of cotton or linen pants and vests should be made available

After removal these should always be washed with soap in hot water

areas should be carefully dried and powdered with talcum powder

### TREATMENT

Before treatment is undertaken precautions against re infection must be organized. The cotton pants and vests used should be such that they cover the whole affected area that is to say in the case of an axillary infection vests with at least short sleeves must be used.

Though the danger of overtreatment does exist it is usually less in this condition than in tinea pedis one reason being that the areas are more sensitive and the immediate pain of strong applications will prevent their over use. When however the areas are actually inflamed strong fungicidal substances must not be applied until the inflammation has been reduced by hot applications alternating with aqueous calamine lotion.

Individuals with a tough skin e.g. negroes and some Indians of the labouring class will usually stand strong applications such as formalin (commercial) and liniment of iodine but even in these individuals care must be exercised and the doctor should himself apply the medicaments not leave this to the patient.

Perhaps the most useful preparation of all is Whitfield's ointment —

B Salicylic acid—gr xxx  
Benzoic acid—gr lx  
Lanolin—½ ounce  
Vaseline—to one ounce

TL

ication half strength  
e possible to use the  
d to discontinue the  
He should also be

warned to apply it to the scrotum very cautiously as it may be exceedingly painful

Alternative applications are 4 per cent gentian violet in 10 per cent alcohol or triple dye. There are also several proprietary preparations e.g. Cignolin—a synthetic chrysarobin preparation—in the form of an ointment or a paint (1 to 3 grains in one ounce of pure acetone) which are useful.

TL

the morning  
In the case  
be made at

A few days of conscientious treatment with any of these applications will usually cure this condition but the treatment must be continued for some time after symptoms have disappeared. Refractory cases will occasionally be encountered in which a succession of medicaments may have to be tried.



## TOKELAU OR *TINEA IMBRICATA*

This infection appears to have a purely tropical distribution. It has been described in India, Ceylon, Burma, Indo China, Malaya, the Dutch East Indies, Borneo, New Guinea, the South Pacific Islands, and China. There are apparently a few foci of infection in Central Africa and in Brazil. In India it is encountered almost solely amongst aborigines in South India, Bengal and Assam and in a few plainsfolk who have been in close contact with aborigines.

### ÆTIOLOGY

This micro-  
biability to  
be trans-  
n the epi-  
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causes further separation

### SYMPTOMATOLOGY

The lesion starts as round or oval macules in the centre of which the horny layer of the epithelium cracks and flakes of epithelium begin to separate from within outwards. The lesion extends and a larger and larger ring of separating white scales is produced. Meanwhile the area in the centre recovers to some extent its normal appearance, but it soon cracks again and a new ring forms within the previous one, so that the lesion eventually consists of a series of concentrically arranged brown (normal skin) and white (separating scales) rings so that the whole skin area suggestive of tattooing. At the periphery the horny layer becomes slightly thickened and raised but there is little inflammatory reaction.

The lesions are very irritating.

Extensive areas of the skin of the trunk and limbs are involved but the hair is not affected. The head, palms, soles, axillæ and groin are seldom affected.

### DIAGNOSIS

Clinical diagnosis  
of the earlier lesions  
simulate ichthyosis but  
found somewhere on the body

### PREVENTION AND TREATMENT

Personal cleanliness is an effective preventive measure. The disease is said not to occur among persons who anoint their bodies with coconut oil.

The lesions themselves respond fairly readily to treatment, but the area involved is so extensive that the whole surface cannot be treated at one time with any of the stronger fungicides. An additional complication is the fact that the patients are mostly uneducated aborigines.

Most fungicides are effective. Castellani's fuchsin paint\* is usually recommended. Dey and Maplestone (1942), who have had considerable

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\* This consists of 10 ccm of a saturated alcoholic solution of basic fuchsin in 100 ccm of 5 per cent phenol in water. Filter this and add 1 gramme of boric acid. After two hours add 5 ccm of acetone and two hours later 10 grammes of resorcinol. Keep in dark stoppered bottles.

experience with this infection, recommend a paint of one drachm each of resorcinol and glacial acetic acid in one ounce of compound tincture of benzoin

## PITYRIASIS (TINEA) VERSICOLOR

This is such a common infection in Indians of the poorer classes that they are usually quite unconscious of its existence and are often unable to appreciate the fact that their skin is not normal, even when the lesions are pointed out to them. It has a wide distribution amongst natives in other tropical countries. It is much less common in fair-skinned persons, but does occur, and it is not strictly confined to hot countries though it is much commoner in them.

Although this infection is widespread in certain social groups, it is not highly contagious and needs close association before it is transmitted from one person to another.

### ÆTIOLOGY

It is caused by *Malassezia furfur*. The fungus invades the superficial layer of the epithelium and causes a fine scaling. There is practically no inflammatory reaction.

### SYMPTOMATOLOGY

The visible lesions are actually accumulations of fungus on the skin, where they form yellowish or brownish plaques. On the brown skin, they appear as a whitish layer of powder, and on the white skin they produce brownish patches. As well as the surface lesions there is apparently some change in the underlying pigment, a decrease in the brown skin and an increase in the fair one. The lesions commence as small macules the size of a pin's head, they increase in size and coalesce. There is a fine powdery desquamation if the affected area is rubbed.

The distribution of the lesions is very characteristic. It corresponds to an area on which dandruff would naturally fall from the hair, that is to say, over the shoulders, on the front and back of the chest, and on the outer aspects of the arms. Sometimes they also appear on the abdomen, neck and face, but seldom on other parts of the body. These are not the covered areas, in the class of individual who usually suffers from this condition, as some writers state. The distribution seems to suggest that the hair may be an important source of infection.

### DIAGNOSIS

The condition is readily recognized clinically but confirmation can be obtained easily by taking a scraping from the area, macerating it in potassium hydroxide and examining it under the microscope. The grape like clusters of spores will be seen.

### TREATMENT

For this superficial infection, the affected area should be rubbed with some other

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### ÆTIOLOGY

The causal organism is *Trichophyton concentricum*. This micro-organism differs from others of this group by its apparent inability to survive saprophytically for any length of time, so that it can only be transmitted by direct contact. It penetrates the epidermis, between the epidermis and the dermis it multiplies abundantly, causing the former to separate, and in due course it penetrates the newly formed epidermis and causes further separation.

### SYMPTOMATOLOGY

The lesion starts as round or oval macules in the centre of which the horny layer of the epithelium cracks, and flakes of epithelium begin to separate from within outwards. The lesion extends and a larger and larger ring of separating white scales is produced. Meanwhile, the area in the centre recovers to some extent its normal appearance, but it soon cracks again and a new ring forms within the previous one, so that the lesion eventually consists of a series of concentrically arranged brown (normal skin) and white (separating scales) rings, so that the whole skin area suggestive of tattooing. At the periphery the horny layer becomes slightly thickened and raised but there is little inflammatory reaction.

The lesions are very irritating.

Extensive areas of the skin of the trunk and limbs are involved but the hair is not affected. The head, palms, soles, axillæ and groin are seldom affected.

### DIAGNOSIS

Diagnosis is usually easy on account of the unique appearance. Thickened edges will sometimes be found somewhere on the body.

### PREVENTION AND TREATMENT

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### DIAGNOSIS

The condition is readily recognized clinically but confirmation can be obtained easily by taking a scraping from the area, macerating it in potassium hydroxide and examining it under the microscope. The grape-like clusters of spores will be seen.

### TREATMENT

This presents little difficulty. Most fungicides will destroy this superficially situated fungus very easily. The commonest application is sodium sulphite 10 to 25 per cent solution. This is washed over the affected area after it has been bathed and well scrubbed. Or an ointment containing 3 per cent salicylic acid and 6 per cent precipitated sulphur can be rubbed in. The hair should be washed also and the sulphite lotion or some other suitable antiseptic applied to it.

The condition will usually clear up within a few days but treatment must be continued for several weeks, and all the usual precautions regarding the changing and sterilization of clothes must be taken if relapse and re-infection are to be obviated

## LEUCODERMA OR VITILIGO

**Definition**—Leucoderma or vitiligo is an acquired condition in which in certain areas there is complete loss of skin pigment, it is characterized clinically by the appearance of ivory-white patches surrounded by an area of normal or increased pigmentation. It is neither infectious nor hereditary, though at times it seems to show a familial tendency

### EPIDEMIOLOGY

It appears to be much more common in tropical countries, but it occurs throughout the world, in people of all races, all ages and both sexes

### ÆTIOLOGY

The cause of leucoderma is not known. It is usually classed as a tropho-neurosis. In India, it has been observed that in the majority of the cases there is some intestinal infection—protozoal, bacterial, or helminthic—and it has been suggested, on rather slender experimental evidence, that the condition may be due to a disturbance of the suprarenals and leucoderma are related. It is seldom encountered in the presence of hypo-adrenia.

### PATHOLOGY

Apart from the total absence of pigment, the affected skin is not changed in any way, the activities of the sweat and sebaceous glands are uninfluenced, but the hair shafts in the affected area sometimes lose their pigment and become whitish or yellowish in colour.

### SYMPTOMATOLOGY

The lesions appear as small white macules and extend slowly. The margins may remain clear-cut, but in the larger patches they tend to become less sharply defined. Sometimes there is an increase of pigment in the adjoining areas, but there is seldom a definite ring of hyperpigmentation around the leucodermic patches.

In the well-developed case the lesions can be classified into several types—(a) the muco-cutaneous type affecting the lips, eyelids and external genitals, (b) the pressure type affecting such areas as the waist when there is continuous pressure from clothes, the *dhoti*, the *sari*, or the belt, (c) the symmetrical type and (d) the generalized type, where the white patches fuse to form large lobulated areas and even progress so far that the original skin coloration is completely obliterated.

The condition may remain stationary for years but is generally slowly progressive in its course, in exceptional instances the patches disappear spontaneously. There are no somatic symptoms associated with this condition but the mental effect of the grotesque disfigurement that may be

produced is often profound. The lesions give rise to no subjective symptoms, but the whitened patches are hypersensitive to heat, and tend to become inflamed readily when exposed to the sun.

### DIFFERENTIAL DIAGNOSIS

The diagnosis does not usually present much difficulty but it is necessary to exclude certain other conditions in which there is complete or partial depigmentation, namely (a) the congenital condition, partial albinism, (b) the bacillary infection, leprosy, (c) the mycotic infection, pityriasis (ii) atrophic macular the protozoal infection conditions of unknown

(a) In partial albinism, the lesions are congenital there is never any bordering of the depigmented patch by hyperpigmented skin and the patient always has a blue iris

(b) In leprosy, the lesions are usually accompanied by sensory loss and the patient has a positive Wassermann reaction and possibly some slight response to arphenamine

(c) In atrophic macular syphilis there is a history of the earlier lesions of this condition which are characteristic and quite unlike leucoderma there is usually a positive Wassermann reaction and possibly some slight response to arphenamine

(d i) In atrophic macular syphilis there is a history of the earlier lesions of this condition which are characteristic and quite unlike leucoderma there is usually a positive Wassermann reaction and possibly some slight response to arphenamine

(d ii) Melano leucoderma generally affects the palms and the soles and rarely the lips it manifests itself by the appearance of patchy leucoderma and melano-

(e) In morphea, the skin shows different grades of depigmentation with smooth, shiny atrophic patches adherent to the underlying tissue

(f i) In morphea, the skin shows different grades of depigmentation with smooth, shiny atrophic patches adherent to the underlying tissue

(f ii) In lupus erythematosus the leucoderma like depigmentation which is permanent, is usually accompanied by a positive Wassermann reaction and possibly some slight response to arphenamine

### TREATMENT

This is far from satisfactory and many writers dismiss the condition as incurable. However at the Calcutta School of Tropical Medicine over a

period of years the routine procedure indicated below has been worked out, this appears to give satisfactory results in a small percentage of cases (Panja\*, 1941, and Panja and Maplestone, 1940)

**A General treatment**—The stools are examined repeatedly for evidence of any intestinal infection, amœbic, bacillary or helminthic. If such an infection is found the appropriate course of treatment is given. As in addition there is frequently a non-specific bowel disturbance suggestive of excessive fermentation, half to one drachm of liquor hydrargyri perchloridi (BP) is given twice daily after meals, in courses of three to four weeks with intervals of one to two weeks, for a period of at least three to six months.

**B Diet.**—The patient is advised to avoid food that is likely to cause intestinal fermentation, and to take germinating gram, beans and peas which are rich in vegetable protein and yield a good supply of tyrosin, a precursor of melanin.

**C Local treatment**—Oil of bouchi (*Psoralea corylifolia*) is rubbed gently on the lesion twice a day for 5 to 10 minutes each time. Sometimes the oil produces intense redness, burning and even vesication after a few

the skin has recovered  
olive oil, either 1 in  
be applied again  
to use the oil at all even in higher dilutions

may appear after 24  
at  
itches  
When  
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possible

In young children the diluted oil should be applied from the beginning

To certain tender parts, such as the muco-cutaneous junctions of the lips, eyelids and external genitals, only the diluted oil should be applied.

The bouchi oil applications are thought to cause a local stimulation of the melanoblasts, the pigment begins to appear after a time, at first as tiny spots on the margin of the patch or in the regions of the hair follicles from where it may spread to repigment the whole lesion.

An alternative procedure is to inject sterilized bouchi oil intradermally into the lesion with a tuberculin syringe and a fine needle, in individual amounts of 0.05 to 0.1 c.c. The number of injections will vary with the size of the depigmented patch, small spots of 1 cm. or so in diameter only need a single injection in the centre, in larger patches the injections are spaced 1 cm. or so apart, until the whole area is covered. In two to three

be observed at the site of the needle puncture  
second and, if necessary,  
immediate white patches,  
the patch to be treated

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ions  
The  
also

injections are painful so that too many cannot be given. The injection is sometimes followed by a small focal ulcer and if several ulcers occur close together they may coalesce and form a relatively large

\* This useful paper has been quoted freely in this section

lesion. It should however be noted that, apart from the extra discomfort at the time and the subsequent scarring, ulceration does not adversely affect the final result, as the scar usually becomes pigmented.

Bouchi oil is an old Indian remedy for the condition, but it seems questionable whether the reaction is a specific one.

#### PROGNOSIS

This is very uncertain, a relatively small percentage of patients show improvement when they persevere with the treatment.

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## HELMINTHIC INFECTIONS

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**Introduction**—The metazoa that parasitize man differ from man's other parasites, the protozoa, the spirochaetes the bacteria and other fungi, the rickettsiae, and the filtrable viruses, in several important directions. Firstly, with few exceptions, they are unable to complete a cycle of development and multiply in a single individual host, or even, except in a very few instances, in one host species, but require one or more intermediate hosts. Secondly, they are usually host species specific, and are acquired by the host in a definite position. Thirdly, they induce some general and local tissue responses in the host, but these are not comparable in their effects to the exo-toxins and endo-toxins, of bacteria for example but helminths, on the other hand, because of their size (all adult helminths are visible to the naked eye) often cause local damage to the tissues, obstruct the normal body functions and deflect the nutrition of the host.

Let us consider how these fundamental differences between metazoa and other parasites are reflected in the epidemiology pathology, symptomatology, prevention and treatment of the diseases that are caused by metazoa.

### EPIDEMIOLOGY

The distribution of most helminthic infections tends to be very limited because the climatic and other local conditions must be suitable not only

for the parasite itself during its exogenous phase, but often for one or more intermediate hosts. Also, the complicated life cycle of the parasite is often dependent for its completion on certain special (and, in our Western way of thinking, unusual) habits of the affected population.

However, neither of these limitations applies in the cases of the hel-

*Trichocephalus trichiurus* and *Ascaris lumbricoides* are also cosmopolitan helminths, but are dependent to some extent on suitable exogenous conditions and, therefore, other things (e.g. sanitary conditions) being equal they are more common in humid tropical climates.

The helminths that have an encysted stage in some human food substance (e.g. *Clonorchis sinensis*, *Paragonimus westermani*, and the large tapeworms) will naturally be limited to those population groups where the consumption of the particular food substance in which these worms encyst is common and, also, to those persons in the population groups who are in the habit of eating the food raw or insufficiently cooked.

The transmission of helminth infections is dependent not only on warm climates but also on the habits of the people. These habits are often defective ones. These defects are as the majority of the population go bare-footed. There

is, however, another habit factor that comes in here—the disposal of excreta. Where the practices in this respect are unsatisfactory, as in India where villagers defæcate in the open fields around the village, or in China where human excreta is used as manure, infections by this group, amongst others, are likely to be very prevalent.

The filarial group of infections are dependent on certain arthropod intermediate hosts, as well as on favourable climatic conditions for their development with

by several very different means. The distribution of these infections is very wide, whereas *Onchocera volvulus*, whose intermediate host is the less common gnât *Simulium damnosum*, is confined within much narrower geographical limits, and *Dracunculus medinensis*, which is dependent for its transmission on a very special set of circumstances regarding drinking-water supply, as well as on the presence of cyclops (and the absence of fish that will prey on them) in the wells, has a very limited distribution, even in countries that are climatically suitable for its transmission.

on the habits of the people of the total

infections such as on indirect especially in the year but man manure infections in *nolepis nana* personal con amongst the

people of India as a whole, on account of eating Hookworm infection, the dwelling, is very common in common than under similar climate are not thus wasted, though some manure in the latter country.

TABLE XV

Phylum	Class	Sub-class	Order (or group)	Sub-order	Super-family	Genus	Species		
NEMATHELMINTHES	NEMATODA		Aphamadia		Trichinelloidea	Trichinella Trichocephalus	spiralis trichinurus	1 2	
			Pharmadia		Rhabdioidea	Strongyloidea		stercoraria	3
					Strongyloidea	Ancylostoma Ancylostoma Necator Gnathostomum	brasiliense duodenale americanum apiostomum	4 5 6 7	
					Trichostrongyloidea	Trichostrongylus	app	8	
					Oxyuroidea	Enterobius	vermicularis	9	
					Ascaridea	Ascaris	lumbricoidea	10	
					Spiruroidea	Gnathostoma	spinaigerum	11	
					Filarioidea	Wuchereria Wuchereria Onchocerca Acanthocheilonema Loa Mansonella	bancrofti malaya volvulus perstans loa ostardi	12 13 14 15 16 17	
						Dracunculoides	Dracunculus	medinensis	18
				Strigosa		Schistocephaloidea	Schistocephalus Schistocephalus Schistocephalus	laminatum marsoni japonicum	19 20 21
			Amphistomata			Paramphistomatoidea	Gastrotrichoidea	laminata	22
			Proscotomata			Fascioloides	Fasciola Fasciolopsis	hepatica bubali	23 24
					Echinocephaloidea	Echinocephalus	app	25	
				Diplostomata	Heterophyidae	Heterophyes Metagonimus	heterophyes yokogawai	26 27	
PLATHHELMINTHES	TREMATODA	DIGenea	Proscotomata						
CESTODEA	CEPHYODA		Pseudophyllidae		Bothrocephaloidea	Diphyllobothrium	latum	28	
			Cyclophyllidae	(Super family)	(Family)	Tenina Tenina Echinococcus	solium argentea granulosus	29 30 31	
				Teninoidea	Hymenolepidae	Hymenolepis Hymenolepis	nana diminuta	32 33	

vectors is dependent mainly on favourable climatic conditions and is common amongst the densely packed populations in many areas in both India and China. Finally, infections that depend on the consumption of raw fish and meat (about one-third of those included in Table XV) are uncommon in India as a large percentage of the population is vegetarian.

On the whole, therefore, China provides an infinitely wider field of interest to the helminthologist than does India.

## PATHOLOGY

The inability of most human helminthic parasites to complete a cycle of development within a single human host means that an helminthic infection is not susceptible to numerical increase within the individual host, and that the weight of the infection, and therefore the extent of the patho-

TABLE XV—Cont

Intermediate host or hosts	Exogenous free-living habitat	Definitive hosts other than man (Reservoir)	Portal of entry Mouth or Cutaneous	Infective medium	Main sites of pathogenic processes	Temperature Common to Warm climates
1 Pig rat, bear	—	Pig rat, bear	M	Pork	G-I tract muscle brain etc	T
2 —	Soil	—	M	Veg*	Lower ileum caecum	C
3 —	Soil	—	C	Soil	Skin, lungs G-I tract	W
4 —	Soil	Hog	C	Soil	Skin	W
5 —	Soil	—	C	Soil	Skin lungs G-I tract	W
6 —	Soil	—	C	Soil	Skin lungs G-I tract	W
7 —	7	Monkey	M	?	Caecum	W
8 —	Soil	—	—	Soil	Intestine	W
9 —	—	—	M	Fingers*	Caecum	C
10 —	Soil	—	M	Food*	Lungs, intestine	C
11 Cyclops & fish	Water	Feline, dog	M	Fish	Skin subcuticle	W
12 Mosquitoes	—	—	C	M bite	Skin lungs lymphatics	W
13 Mosquitoes	—	—	C	M bite	Lymphatics	W
14 S. mulum	—	—	C	S-bite	Subcuticle cornea	W
15 Culicoides	—	—	C	C-bite	(Serous cavities)	W
16 Chrysops	—	—	C	C-bite	Subcuticle conjunctiva	W
17 Culicoides	—	—	C	C-bite	(Serous cavities)	W
18 Cyclops	Water	Cattle dog	M	Water	Lung & subcuticle skin	W
19 Snails	Water	—	C	Water	Skin lung liver bladder	W
20 Snails	Water	—	C	Water	Skin lung liver colon	W
21 " " "	" " "	" " " "	"	"	"	"
22 " " "	" " "	" " " "	"	"	"	"
23 " " "	" " "	" " " "	"	"	"	"
24 " " "	" " "	" " " "	"	"	"	"
25 " " "	" " "	" " " "	"	"	"	"
26 Snails & fish	Water	Cat dog fox	M	Fish	Small intestine	W
27 Snails & fish	Water	Cat seal pebrum	M	Fish	Small intestine	W
28 Snails & fish	Water	Dog cat seal	M	Fish	Liver pancreas	W
29 Snails & fish	Water	Dog cat seal	M	Fish	Liver	W
30 Snails & crabs	Water	Cat dog pig	M	Crabs	Lung	W
31 Fish & cyclops	Water	Canine felinae	M	Fish	G-I tract	T
32 Pig	Soil	—	M	Pork*	G-I tract muscle brain etc	C
33 Cattle	Soil	—	M	Beef	G-I tract	C
34 Man sheep	—	Dog	M	Fingers*	Liver lung brain	C
35 —	—	Rodents	M	Fingers*	Small intestine	C
36 Arthropods	—	Rodents	M	Food	Small intestine	C

\* Indicates that the egg is the infective stage

genesis, will usually be dependent on the number of parasites that enter the host, rather than on the tissue reactions of the host, which so often are the determining factors in the production of disease by non metazoal parasites

The pathological responses of the host to helminthic infections are usually allergic rather than anti-toxic in nature

### SYMPTOMATOLOGY

In the majority of helminthic infections, the presence of only a few parasites will not cause pathological lesions of sufficient importance to produce clinical evidence of infections, so that in circumstances of low endemicity the vast majority of the helminthic infections will be symptomless. It is only when the initial invasion is exceptionally heavy or when the individual is subjected to repeated invasions that these infections reach the clinical threshold, and it is even less frequently that the diseases caused by helminths reach an acute stage. Another result of this poor host-tissue response is seen in the long duration of most helminthic infections.

### PREVENTION

The complex life cycles of most helminths apparently display several Achilles heels, but in practice it is found that these points are not usually as vulnerable as one would at first suppose, because of ingrained customs of the affected population groups. To take some examples from the infections mentioned above, hookworm infection could be obviated by proper sanitary disposal of faeces or by the use of proper footwear, clonorchiasis and taeniasis by the avoidance of undercooked fish and meat, dracontiasis by keeping wells covered or by drinking only filtered or boiled water, and filariasis by avoiding mosquito bites. But in each case it will be many decades and in some cases probably centuries before it will be possible to impress on the population groups most affected, the necessity for altering their habits to fulfill these apparently simple requirements. This establishes a wide gap at the top of the list of preventive procedures than in the case of

### TREATMENT

In the treatment of bacterial and other infections we usually have to rely largely on the host-tissue reaction and are often content to stimulate or bolster these rather than to attempt direct action against the parasite. In helminthic infections, however, the relative poverty of the host-tissue response compels us to use drugs. In the case of the blood parasites it is more difficult though some progress has been achieved, but with the lymph and tissue parasites it presents a problem that has in no case yet been satisfactorily solved.

### CLASSIFICATION

Some form of classification of helminthic diseases is desirable, at least as a concession to the scientists' natural desire for order, if not as an aid to memory for the student. Classification might be along several lines, some of these will be considered —

1. Classification according to the taxonomic relations of the causal agents.

*saginata* and *Echinococcus granulosus*. It is felt, however, that this table which gives an outline of the taxonomy of the majority of the human helminths (some of which are not deemed of sufficient importance to need further consideration in this book) may be of value for reference when the names of classes, subclasses, orders, sub-orders and super-families are mentioned by other writers. It will also save the necessity for any further reference here to the subject of taxonomy.

**II Classification according to the medium of transmission and mode of entry of the causal parasite**—In this classification five groups can be considered

(i) Contaminated fingers and food. This would not be a common source of infection as food tends to sink rapidly, so that any primitive form of sedimentation or filtration will remove them.

(ii) Oral infection through raw food substances that contain encysted larvae.

(iii) Oral infection with water containing infected crustaceae.

(iv) Cutaneous infection by active entry of the pre-adult forms (larvae or cercariae) from water. In several instances the entry may also occur through the mucous membranes of the buccal cavity or pharynx but in no case is this the important route of infection.

(v) Cutaneous infection by entry of larval forms conveyed by arthropods.

The arrangement of the important helminths according to this classification is shown in the table below.

TABLE XVI

Showing Helminthic Parasites Arranged according to their Portal of Entry and the Medium of Transmission

Portal of entry	Medium of transmission	Species
Oral	Fingers and contaminated food	<i>Trichuris trichiura</i> <i>Ascaris lumbricoides</i> <i>Oesophagostomum apistomum</i> <i>Hymenolepis nana</i> <i>Echinococcus granulosus</i> <i>Enterobius vermicularis</i> <i>Trichostrongylus</i> spp <i>Hymenolepis diminuta</i>
	Special food substances containing encysted larvae	<i>Trichinella spiralis</i> <i>Fasciola hepatica</i> <i>Echinostoma</i> spp <i>Metagonimus yokogawai</i> <i>Clonorchis sinensis</i> <i>Tenia solium</i> <i>Diphyllobothrium latum</i> <i>Gnathostoma spinigerum</i> <i>Fasciolopsis buski</i> <i>Heterophyes heterophyes</i> <i>Opisthorchis felinus</i> <i>Paragonimus westermani</i> <i>Tenia saginata</i> <i>Gastrodiscoides hominis</i>
	Water containing infected crustaceae	<i>Dracunculus medienensis</i>
Cutaneous	Active invasion by larvae or cercariae from soil or water	<i>Strongyloides stercoralis</i> <i>Ancylostoma braziliense</i> <i>Schistosoma harnadobrium</i> <i>Schistosoma japonicum</i> <i>Ancylostoma duodenale</i> <i>Necator americanus</i> <i>Schistosoma mansoni</i>
	Invasion by larvae conveyed by arthropods	<i>Wuchereria bancrofti</i> <i>Acanthocheilonema persians</i> <i>Onchocerca volvulus</i> <i>Wuchereria malaia</i> <i>Loa loa</i> <i>Mansonella ozzardi</i>

III *Classification according to the parasitological findings.*—This is shown in tabular form below —

TABLE XVII

*Showing Helminth Infections Arranged According to the Clinical Parasitic Findings  
A Diagnostic Classification*

Stage	Material	Species	
eggs	(i) In faeces		
	(a) Constant, in large numbers	<i>Trichuris trichiura</i> <i>Ancylostoma duodenale</i> <i>Necator americanus</i>	<i>Ancaris lumbricoides</i> <i>Trichostrongylus</i> spp <i>Fasciolopsis buski</i>
	(b) Periodic or scanty	<i>Schistosoma mansoni</i> <i>Gastrodiscoides hominis</i> <i>Heterophyes heterophyes</i> <i>Opisthorchis felinus</i> <i>Clonorchis sinensis</i> <i>Diphyllobothrium latum</i> <i>Hymenolepis nana</i>	<i>Schistosoma japonicum</i> <i>Fasciola hepatica</i> <i>Echinostoma</i> spp <i>Metagonimus yokogawai</i> <i>Cesophagostomum</i>  <i>Hymenolepis diminuta</i>
	(c) Rare	[ <i>Schistosoma hematobium</i> ] [ <i>Paragonimus westermanni</i> ] [ <i>Tania solium</i> ]	[ <i>Enterobius vermicularis</i> ]  [ <i>Tania saginata</i> ]
	(ii) In a perianal swab	<i>Enterobius vermicularis</i>	
	(iii) In the urine	<i>Schistosoma hematobium</i>	
	(iv) In the sputum	<i>Paragonimus westermanni</i>	
	(i) Faeces	<i>Strongyloides stercoralis</i> [ <i>Trichinella spiralis</i> ]	[ <i>Ancylostoma duodenale</i> ] [ <i>Necator americanus</i> ]
	(ii) Blood	<i>Wuchereria bancrofti</i> <i>Acanthocheilonema perstans</i> <i>Mansonella ozzardi</i>	<i>Wuchereria malays</i> <i>Loa loa</i>
larvae	(iii) Discharge from ulcers	<i>Dracunculus medinensis</i>	
	(iv) In subcutaneous tissues, or muscle	<i>Onchocerca volvulus</i> <i>Trichinella spiralis</i>	
	(v) In cysts	<i>Echinococcus granulosus</i>	
adult worms or proglottids	(i) In faeces	<i>Tania solium</i> [ <i>Diphyllobothrium latum</i> ]	<i>Tania saginata</i>
	(ii) In subcutaneous tissues	<i>Gnathostoma spinigerium</i> [ <i>Loa loa</i> ] [ <i>Onchocerca volvulus</i> ]	

*Note* The brackets indicate that the species also appears under another heading but is more important from a practical diagnostic point of view

Other classifications that might be adopted would be

IV *According to the nature of the intermediate host or hosts, of the definitive hosts other than man, and/or of the habitat of the free-living phase,*

V *According to whether they are infections of warm, or of temperate countries, or are cosmopolitan in their distribution,*

VI *According to the main sites of the pathological processes that they engender*

## HELMINTHIC INFECTIONS

There is little to be gained by regrouping the worms according to the last three classifications but in the second half of Table XV these data are tabulated.

None of the above classifications would appear to be entirely satisfactory for the purpose of this book, but the following modification of the pathological classification, seems to allow a consecutive presentation of the subject and has therefore been adopted here.

### CLASSIFICATION ADOPTED

**A. Intestinal parasites**—These can be divided into several groups:

(i) Nematode worms whose portal of entry is the mouth, whose infective stage is the egg, whose cycle is a relatively simple one and does not include an intermediate host, and whose distribution is cosmopolitan. In this group are included *Trichuris trichiura*, *Enterobius vermicularis*, *Ascaris lumbricoides*, and they are described under the general heading 'Cosmopolitan intestinal nematode infections'.

(ii) Nematode worms whose usual portal of entry is through the skin, whose infective stage is the filariform larva, whose life cycle, though it does not include an intermediate host, requires special exogenous conditions and whose distribution is mainly tropical. In this group are included *Ancylostoma duodenale*, *Ancylostoma braziliense*, *Necator americanus*, *Strongyloides stercoralis*, and *Trichostrongylus* spp., though the usual portal of entry of the last named is not known, it is apparently capable of entering through the skin or the mouth. They are described under the heading 'Tropical intestinal nematode infections'.

(iii) The tapeworms, *Diphyllobothrium latum*, *Taenia solium*, *Taenia saginata*, *Hymenolepis nana* and *Hymenolepis diminuta* which are not a very homogeneous group in their life cycles, though their portal of entry is in each instance the mouth, and except in the case of *H. nana*, they enter in the larval stages, they are cosmopolitan in their distribution. They are described under the heading 'Tapeworm infections'.

(iv) *Trichinella spiralis* which must be considered here because its adult stage is in the intestinal mucosa and produces intestinal symptoms though the larval stage causes more serious symptoms in the same individual host. Infection is by ingestion of the encysted larval stage in meat. It is an infection of temperate zones. This is described under the heading 'Trichinosis'.

(v) The intestinal trematodes, of which only one *Fasciolopsis buski* is described here. These worms have a complex life cycle, they usually enter their determinative hosts in their larval stage and are tropical in their distribution. (*Fasciolopsis buski* will be described more appropriately with the other flukes.)

**B. Parasites of lymphatics, subcutaneous tissues and serous cavities**—These can be divided into three groups—

(i) *Wuchereria malaya*, *Onchocerca* spp. and *Mansonella* spp. are transmitted to man by the agency of blood-sucking insects and are described under the heading 'Lymphatic filariasis'.



# ASCARIASIS

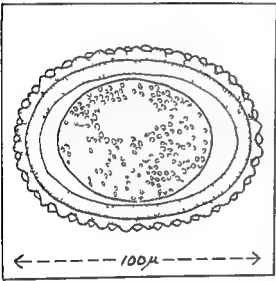
## EPIDEMIOLOGY

This is a cosmopolitan infection, but, because the climatic conditions in tropical countries are more favourable than those of temperate and cold countries to the exogenous phase of this worm, and, because on the whole the populations of the former adopt a lower standard of both personal and environmental hygiene, the infection is widespread and heavy one amongst the inhabitants of most tropical countries

Ascariasis is a good indicator of the sanitary advancement in any population, and in temperate countries it is confined mainly to insanitary population groups and is particularly prevalent amongst poorer class children

## ÆTIOLOGY

The causal organism—*Ascaris lumbricoides* is the only species of the genus which infects man. *Ascaris suum* of the pig is morphologically identical, but physiologically distinct and mutual interchange of hosts apparently does not occur



The egg is the infective stage. The fertile egg which measures 45 to 75 microns by 35 to 50 microns, has a thick but transparent coarsely mammillated albuminoid shell, it is unsegmented and it contains an almost globular protoplasmic mass of moderate sized regular granules

The larvæ develop inside the egg and pass through two stages before they emerge. The larva that eventually emerges from the egg is 0.2 to 0.3 millimetres in length by 0.014 mm in diameter, it passes through two more developmental stages and increases to 1 to 2 millimetres in length

The adult is a large round worm, the male is 15 to 31 mm by 2 to 4 mm in diameter and the female 20 to 35 by 3 to 6 mm but is occasionally longer

Figure 142 The fertile egg of *Ascaris lumbricoides*

The life cycle—Mature (embryonated) eggs are ingested in the duodenum the shells split and active embryos emerge these penetrate the mucous membrane of the intestine and enter a lymphatic vessel or venule\*

\* There is experimental evidence for this (Ransom and Cram 1921). If however the larvæ (about 14 microns in diameter) travel via the venules they will have to pass through the liver whereas if they travel via the lymphatics they will miss the liver. There is no evidence of any damage is considerable. It is possible that this is development in the latter organ or it may develop in the lymphatics and miss the liver

to reach the right side of the heart and the lungs in the blood stream, in the lungs the larvae moult twice during a sojourn of several days, and eventually they penetrate into an alveolus whence they migrate up the trachea and down the œsophagus to reach the intestine once more and become adults. In their larval stages they live on blood, but the adults are almost entirely lumen feeders. The female lays eggs at the rate of nearly a quarter of a million a day, these are passed out with the stools, and mature in the soil. The adult worms may live for at least 15 months.

**Conditions favouring transmission**—A moderately high temperature

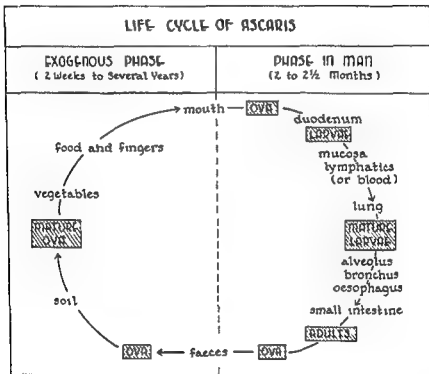


Figure 143

(80° F) favours the exogenous phase of the worm and though the eggs will survive drying and may be blown about in dust they reach maturity earlier in a warm humid environment.

The infection is acquired from the faeces contaminated ground by means of soiled hands and other objects that children frequently place in their mouths, contaminated food particularly vegetables in the growing of which human excreta have been used as manure and from contaminated water supplies.

#### PATHOLOGY

This is not as clear-cut as in many other helminthic infections.

The migrating larvae during their sojourn in the lungs damage the capillaries and cause a cellular, largely eosinophilic, reaction, there is des-

quamation of the alveolar epithelium, bleeding into the alveoli, and often in heavy infections a pneumonitis or a true pneumonia resulting from secondary bacterial infection

Blood-stained sputum containing ascaris larvae may be coughed up

Aberrantly migrating larvae may produce thrombotic lesions in various organs, including the brain and the cord, but such instances are rare

The adults in the intestinal canal do not cause any gross pathological lesion as a rule, but when the infection is very heavy, they may wander into other organs, e.g. the gall-bladder, liver, bronchus, or even eustachian tube, and produce considerable local disturbances, or in the intestine itself, they may become impacted causing obstruction, directly or as a result of intussusception, and even perforation. They also produce a 'toxin', apparently an albumose with neurotoxic, anaphylactic, anti-peptic, and other properties, especially after they are dead, that causes a local reaction in the bowel, and is absorbed, producing a 'toxæmia' that may be fatal in ill-nourished children

The writer has removed half a bucketful of worms from the intestinal tract of a patient who died of intestinal obstruction, they were aggregated in solid knots in different parts of the intestinal tract. There were certainly a thousand round worms, but the record is apparently held by Ryrie who counted 1488 from one patient.

**Blood picture**—There is usually an eosinophilia, often up to 1,500 (or 20 per cent) per c mm, but the degree of eosinophilia is no indication of the weight of the infection

#### SYMPTOMATOLOGY

The symptoms produced are very variable in degree and very protean in character. In the majority of light infections, there are probably no symptoms due to the ascaris, but some observers believe that in children even these light infections frequently cause intellectual retardation, stunted growth, and general sub-health

In heavy infections, during the stage of migration the larvae may undoubtedly cause pneumonitis and pneumonia, and more rarely the conditions that result from embolism in the various organs and tissues referred to above

During their intestinal phase, the adults cause vague abdominal pains indigestion nausea and vomiting, malnutrition, pallor (not necessarily associated with anæmia) and heavy rings under the eyes, restlessness and insomnia and, in infants, convulsions and death, as well as the symptoms produced by the worms when they wander into other organs, e.g. suffocation when they obstruct the bronchi, and peritonitis when they cause intussusception appendicitis, or perforation

Children are very likely to pass live worms in their stools, or these may escape *per anum* between stools, or be vomited, or escape through the nares, the incident causes considerable alarm to the patient, or the parent, but is not in itself of any special significance beyond indicating the presence of the worms and the probability that there are more

#### DIAGNOSIS

The diagnosis does not ordinarily present any difficulty, as the female passes large numbers of eggs regularly throughout her life, and these can

be readily recognized, though it may be necessary to employ a concentration method. *Ascaris* eggs are not well demonstrated by floatation methods. It is said that a certain percentage of persons, less than 4 per cent, will harbour male worms only, in such cases there will be no ova and diagnosis will be best made by the therapeutic test.

The characteristic *ascaris* egg has been described above, but occa-

### PREVENTION

All-round sanitary improvement will be necessary to prevent or reduce this infection. It will however be advisable to find out which are the most highly infected groups in a population, and then what is the main source of infection, so that special measures may be adopted. It is often a homestead problem in which the infection is maintained by promiscuous defaecation of children, and until this has been corrected the infection will be certain to recur. Education, especially in schools, will be an important means of achieving this.

Mass treatment, in which it will be most essential that all children are included, will effect some improvement by reducing the source of infection, but, unless combined with other sanitary measures, it will not produce any permanent reduction in infection in the population.

### TREATMENT

Santonin, which was at one time looked upon as a specific has little to recommend it, and has now been replaced by other safer and more efficient drugs.

Oil of chenopodium (B.P.) is very effective but is best given with tetrachlorethylene, 1 c.c.m. of the former with 3 c.c.m. of the latter for an adult and for children 0.25 c.c.m. of this mixture for every year of apparent age. This should be given shaken up with an ounce of saturated sodium sulphate solution.

For the safety of the patient it is essential to reduce the dose of oil of chenopodium, as indicated above, in the case of children, but since the worms are the same size whatever the size of the host, the smaller doses may prove inadequate (Maplestone and Mukerji 1938). For this reason, the less toxic hexylresoreinol may be substituted in the case of young children.

Hexylresoreinol is at present available only in the form of the proprietary caprokol crystalloids (Sharpe and Dohme) containing 0.1 gramme or 0.2 gramme each. This is given on an empty stomach (5 hours after food) in doses of 1 gramme (5 x 0.2 g.) for adults and older children. 0.8 gramme for children between 6 and 11 years, and 0.6 gramme for children from 1 to 5 years of age. This dose is followed in two hours by an ounce of saturated sodium sulphate solution (for an adult and less for children).

In the case of either drug if a good reaction is not secured within a few hours the purgative should be repeated, as the early removal of both the drug and the dead worms is very desirable, there is evidence that a toxin may be absorbed from the disintegrating *ascaris*.

The full dose of the former medicine will usually cure 90 per cent of adults, but with the smaller dosage in children the cure rate is not so high. For the latter drug, an all-round 90 per cent cure rate is claimed.

## THREADWORM (PIN-WORM) INFECTION OR OXYURIASIS

### EPIDEMIOLOGY

This infection is world-wide, it is also probably both the commonest and the most harmless of intestinal helminthic infections. It has been shown to be present in 35 per cent of a general population group in Washington (D C, USA) and in nearly 70 per cent in certain children's institutions. Writers usually assume that it will be more common in the tropics, on account of the lower sanitary standards in these countries, but this is by no means a foregone conclusion, as the habits and general mode of life of many inhabitants of the tropics are such that they would be less likely to foster this infection than are those of the natives of more advanced western countries. However, few reliable figures are available.

As well as being an institutional disease, it is a family disease. The highest infection rate will always be found in the children.

### ÆTIOLOGY

The causal parasite, *Enterobius vermicularis* (previously placed in the genus *Oxyuris*, hence the name 'oxyuriasis'), is a very small thread-like nematode worm, the male, which is seldom seen, is 2 to 5 millimetres long by 0.1 to 0.2 mm in diameter and the female, which has a fine pointed tail, is 8 to 12 mm long by 0.3 to 0.5 mm in diameter. The eggs are 50 to 60 microns long by 20 to 30 in diameter, they are ovoid in shape with one side slightly flattened, they have a moderately thick transparent shell, and when seen usually contain a fully-developed embryo.

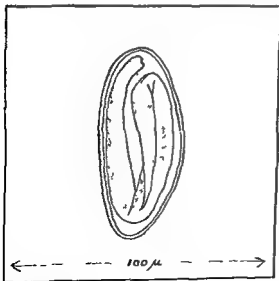


Figure 144 The egg of *Enterobius vermicularis*

Their life cycle is a simple one. The eggs are swallowed, larvae hatch out in the duodenum and pass down the intestinal canal to the cæcum, moulting twice en route, here they develop into adults, they

attach themselves to the mucosa of the cæcum and large intestine, but to oviposit the females migrate outside the intestinal canal. The eggs remain attached to the skin in the grooves around the anus, to the host's clothes, or to the bedclothes, or they fall to the ground where when dry they be

come part of the dust of the room and in an infected household can be recovered in large numbers from the dust lying on furniture or even along the tops of pictures on the wall. The host may reinfect himself by scratching the skin around the anus or the eggs may regain entry into the same host or into other members of the family in innumerable ways and the cycle will commence again.

The cycle takes about two months to complete.

# **PATHOLOGY AND SYMPTOMATOLOGY**

It is quite obvious that in the large majority of infected persons there is no pathogenesis. There is no very convincing evidence that the worm

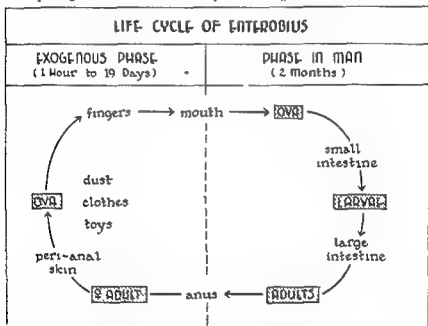


Figure 145

produces any lesions in the intestinal tract catarrhal inflammation mucosal erosions and allergic manifestations in sensitive persons are referred to. Acute and subacute appendicitis are sometimes mentioned in the worms are found in 11 per cent of children showed acute inflammation a population with possibly a 35 very convincing evidence of the predilection for this site.

The female worm however causes anal pruritus which leads to scratching and trauma with the attendant dangers of secondary infection. This will lead to disturbed sleep and irritability and may thus indirectly affect the health of a child.

There is a little evidence that in heavy infections in ill nourished children some invasion of the mucosa may take place with resultant diarr

rhoeal and other disturbances, but with this possible exception it seems very doubtful if any of the varied symptomatology that is popularly attributed to this worm is really caused by it

### DIAGNOSIS

Eggs will not be found in the stools of more than about 5 per cent of infected persons, so that stool examination is useless. To find the eggs it is necessary to take a swab from around the external anal orifice. The best method of doing this is with the NIH (National Institute of Health) swab



The end of the glass rod is passed through the cork of the test tube with the other end of the glass rod passed through the cork with which the test tube is closed. The cellophane swab is wiped

and a coverslip is applied. Under the low power the slide is examined and eggs will be seen lying between the slide and the cellophane and adhering to the latter.

### PREVENTION

The main source of infection lies in the patients themselves and the other members of the household and in their immediate environment. Prevention therefore consists in simultaneous and thorough treatment of every member of a household, combined with a very complete cleaning of the house and the maintenance of a high standard of personal cleanliness. Such measures as providing night clothes that prevent children scratching their anal orifices and transferring

Figure 146  
NIH swab  
(Hall 1937)

certain to take  
not by solved

### TREATMENT

The most satisfactory results are obtained with gentian violet, the dosage is the same as that for strongyloidiasis (see p 632), but it is usual to divide the course into two 8 day periods, leaving an interval of one week between courses (Wright & Brady, 1938). Hexylresorcinol is also very effective, especially if the oral administration (for dosage see ASCARIASIS) is combined with an enema of a 1 in 1,000 dilution of the same drug. After the drug is given and the enema of one pint long as possible, a warm-water bowel wash should be given.

If the above drugs are not available, tetrachlorethylene, as given in hookworm infection (see p 626), will be found relatively satisfactory.

Whatever drug is used in order to test cure perianal swabs should be taken. It is unsafe to assume that the patient is cured until seven such swabs (preferably NIH) have been negative.

## WHIPWORM OR TRICHURIS INFECTION

### EPIDEMIOLOGY

This infection is again world wide but it is probably more common in the tropics especially the humid tropics. It is epidemiologically closely associated with ascaris infection but it is not so widespread and is less prevalent in dry areas. It is more common amongst children than adults.

### ÆTIOLOGY

The causal parasite *Trichuris trichiura* (or *Trichocephalus trichiurus*) measures from 3 to 5 centimetres the male being slightly smaller than the female. It is a whitish grey worm with a filamen-  
tous anterior three fifths and a stouter posterior two fifths this gives it its very appropriate name. The egg measures about 52 by 22 microns it has a double shell the outer one of which is bile stained it is lemon shaped and at each pole there is a hole through the shell that is filled with a non staining substance which like the bung in a barrel projects slightly to make button like prominences at each end.

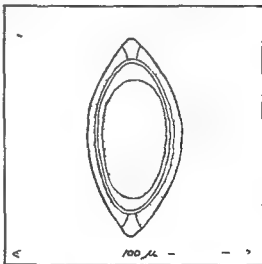


Figure 147 The egg of *Trichuris trichiura*

The life cycle is as follows—Fully embryonated eggs are ingested by man who is the only host and

tance just under the surface in a way that prevents easy mechanical removal. Here the females produce their immature eggs which pass out with the faeces. The developmental phase from egg to adult takes about two weeks under optimal conditions. They are now ready for ingestion but about a year and when they are ingested the cycle starts again.



## PATHOLOGY AND SYMPTOMATOLOGY

These worms appear to produce distinctly more damage in the intestines than do thread worms, and it is also believed that they suck blood. They are occasionally associated with a moderate eosinophilia which suggests the absorption by the host of some allergin, and insomnia, loss of appetite, and 'nervousness' are attributed to them, even when infections are light, but there is better evidence with regard to heavy infections, and it is believed that quite severe anaemia, diarrhoea, emaciation, and a condition somewhat similar to that produced by hookworm infection may occur.

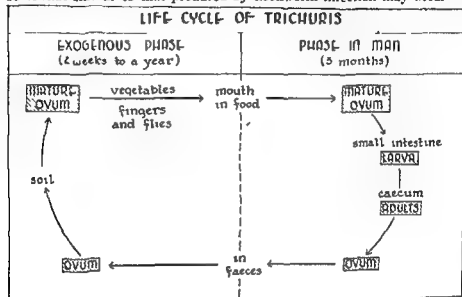


Figure 148

## DIAGNOSIS

... easily in the  
te the search  
are a rough

indication of the degree of infection

## PREVENTION

There are no special measures to be recommended. This infection, like that of ascaris, is a good indication of personal and environmental hygienic practices of a community.

## TREATMENT

There is no specific, available for general use, for the treatment of this infection. All the anthelmintics mentioned above should be tried. It is usually found that heavy infections are reduced by tetrachlorethylene and oil of chenopodium. Light infections are often uninfected. It will be better if there are large numbers of worms and then a high alkaline enema.

There is however one substance that is apparently a specific, namely, leche de higueron, which is the sap of certain species of the genus *Ficus*.

*Ficus glabrata* and *F. doliaria* grow in Central and South America where they are used extensively as anthelmintics. The latex contains a proteolytic ferment, but this can only be preserved under conditions of refrigeration, and it is not yet commercially available outside the countries where it grows (Faust, D'Antoni and Sawitz, 1943). In several countries, e.g. India, attempts have been made to use for this purpose the latex of the local species of *Ficus*, but so far without success. The fresh latex is given in a two-ounce dose on an empty stomach, preferably at night, after thorough cleansing of the bowel by salines and enemata.

The cure is tested by examination of the stools for ova 3 to 5 days after treatment. If they are still present, the treatment should be repeated after a week's interval.

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- |   |   |
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## PATHOLOGY AND SYMPTOMATOLOGY

These worms appear to produce distinctly more damage in the intestines than do thread worms, and it is also believed that they suck blood. They are occasionally associated with a moderate eosinophilia which suggests the absorption by the host of some allergin, and inœmia, loss of appetite, and 'nervousness' are attributed to them, even when infections are light, but there is better evidence with regard to heavy infections and it is believed that quite severe anæmia, diarrhoea, emaciation, and a condition somewhat similar to that produced by hookworm infection may occur.

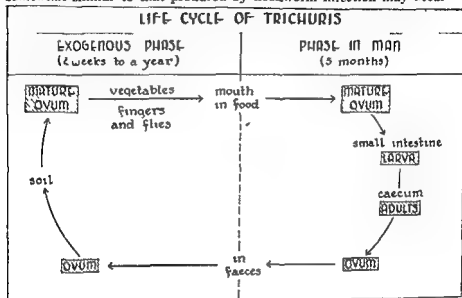


Figure 148

## DIAGNOSIS

indication of the degree of infection

## PREVENTION

There are no special measures to be recommended. This infection like that of ascaris is a good indication of personal and environmental hygienic practices of a community.

## TREATMENT

There is no infection. All the usually found th oil of chenopodium are often uninfused will be better if and then a high alkaline enema.

There is however one substance that is apparently a specific namely, leche de higueron which is the sap of certain species of the genus *Ficus*.

*Ficus glabrata* and *F. doliaria* grow in Central and South America where they are used extensively as anthelmintics. The latex contains a proteolytic ferment, but this can only be preserved under conditions of refrigeration, and it is not yet commercially available outside the countries where it grows (Faust, D'Antoni and Sawitz, 1943). In several countries, e.g. India, attempts have been made to use for this purpose the latex of the local species of *Ficus*, but so far without success. The fresh latex is given in a two-ounce dose on an empty stomach, preferably at night, after thorough cleansing of the bowel by salines and enemata.

The cure is tested by examination of the stools for ova 3 to 5 days after treatment. If they are still present, the treatment should be repeated after a week's interval.

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- WRIGHT W H and BRADY F J (1938) *The Treatment of Oxyuriasis with an Improved Type of Enteric-coated Tablet* *J Parantol*, Supp 24, 9

## PATHOLOGY AND SYMPTOMATOLOGY

These worms appear to produce distinctly more damage in the intestines than do thread worms, and it is also believed that they suck blood. They are occasionally associated with a moderate eosinophilia which suggest the absorption by the host of some allergin, and insomnia, loss of appetite, and 'nervousness' are attributed to them, even when infections are light, but there is better evidence with regard to heavy infections, and it is believed that quite severe anaemia, diarrhoea, emaciation, and a condition somewhat similar to that produced by hookworm infection may occur.

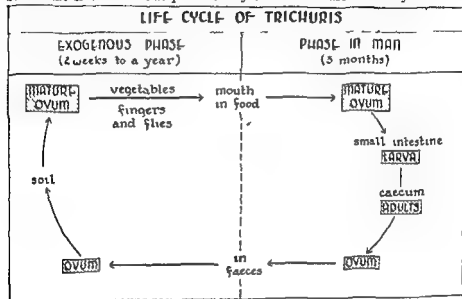


Figure 148

## DIAGNOSIS

This presents no difficulties. The eggs are unmistakable when the infection is light. The indication of the degree of infection

the  
arch  
high

## PREVENTION

There are no special measures to be recommended. This infection, like that of *ascaris*, is a good indication of personal and environmental hygienic practices of a community.

## TREATMENT

There is no specific, available for general use, for the treatment of this infection. All the anthelmintics mentioned above should be tried. It is usually found that oil of chenopodium are often uninfused will be better if and then a high alkaline enema.

There is however one substance that is apparently a specific, namely, leche de higuera, which is the sap of certain species of the genus *Ficus*.

## WHIPWORM OR TRICHURUS INFECTION

*Ficus glabrata* and *F. delavaya* grow in Central and South America where they are used extensively as anthelmintics. The latex contains a proteolytic ferment but this can only be preserved under conditions of refrigeration and it is not yet commercially available outside the countries where it grows (Faust, D'Antoni and Sawitz, 1943). In several countries e.g. India attempts have been made to use for this purpose the latex of the local species of *Ficus*, but so far without success. The fresh latex is given in a two ounce dose on an empty stomach preferably at night after thorough cleansing of the bowel by salines and enemata.

The cure is tested by examination of the stools for ova 3 to 5 days after treatment. If they are still present the treatment should be repeated after a week's interval.

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# TROPICAL INTESTINAL NEMATODE INFECTIONS

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## ANCYLOSTOMIASIS AND HOOKWORM DISEASE

**Definition**—Ancylostomiasis or hookworm infection that is infection by *Ancylostoma duodenale* *Necator americanus*, or *Ancylostoma braziliense* may be symptomless or, if the infection is a very heavy one and/or the subject is undernourished or otherwise particularly susceptible, it may give rise to symptoms of various degrees of severity. The most prominent of these are skin eruptions at the point of entry or along the route of the migrations of the larvae—conditions known respectively as water



(or ground) itch' and 'creeping eruption'—and, when the worms are established in the bowel, anæmia, cardiac dysfunction, gastro-intestinal disturbances, and debility—a symptom complex known as hookworm disease. The infection is transmitted from man to man by faecal contamination of the soil and to man by worms through the skin usually of the feet in warm climates, and occurs in temperate conditions approximately

**Historical.**—There are very early authentic records of the existence of hookworm disease, e.g. in the Ebers Papyrus and unmistakable clinical examples can be traced in the medical writings throughout the ages up to the middle of the 19th century, but the real nature of the disease was not realized prior to 1853 when Bilharz definitely associated 'Egyptian chlorosis' with the presence of the worm described ten years previously by Dubini in Italy and named *Ancylostoma duodenale*.

Wucherer confirmed these observations in Brazil in 1866 where he associated the worm infection with 'tropical anæmia'. Surprisingly, it was another twenty years before Grassi and the brothers Parona showed that the condition could be diagnosed by finding the ova in the stools.

The first serious medical attention was attracted to the disease by the St Gothard tunnel outbreak in 1880. When this tunnel was completed in 1882, the workers were dispersed and many were employed in mines in Central Europe where they disseminated the infection. It was first recorded in tropical countries other parasites, as it frequently is even today.

It was first shown that the infection had undoubtedly been introduced from Europe to the infection was almost entirely absent in tropical Africa first.

In 1893, Looss discovered that the ordinary route of infection was not as had been previously supposed, by the mouth from contaminated food or fingers but through the skin, usually of the feet, whence the larvae migrated via the lymph channels blood stream lungs œsophagus and stomach to the duodenum and small intestine. His epoch-making monograph on this subject was published in 1911.

**Geographical distribution.**—Hookworm infection occurs in practically all humid tropical countries and in a number of subtropical areas in both the northern and the southern hemispheres. Several outbreaks have been reported in temperate countries in mines and tunnels, where the temperature and humidity conditions simulate those prevalent in tropical countries.

It occurs in the southern states of North America, throughout Central America, and in South America—in Venezuela, the Guianas, Brazil, Paraguay, Uruguay, and Argentina—as far south as Buenos Aires, but not in the countries on the west coast. It occurs throughout the west coast of tropical Africa, on the east coast in Tanganyika and Portuguese East Africa and in Madagascar. *Necator americanus* is the only important human hookworm in all these countries, except for a few areas in southern Brazil, in Paraguay, in Panama, and in Portuguese West Africa, where, although the infection is predominantly *Necator americanus*, *Ancylostoma duodenale* occurs also.

*Ancylostoma duodenale* is solely responsible for the infections in Egypt, in North Africa, especially Tunisia, in southern Italy and Sicily, and in the mines in Spain and countries in Europe where the infection still persists.

In Asia, infection is widespread in India, southern China, Burma, Siam, Indo-China, Malaya, the Dutch East Indies and Japan, Borneo,

the Philippines, and New Guinea, and in Queensland in Australia. In most of these areas both species are found

In India, there are few areas throughout the plains free from the infection, but in very few places does it assume serious proportions. Some of the coastal areas in southern India and Ceylon are exceptions, here the infections are almost solely *Necator americanus*, and in Ceylon in particular it has been a very serious public health problem. In northern India, the infection is mainly *Ancylostoma duodenale* and in the central portion of the country and in the north-east provinces both worms are found but the former certainly predominates

*Ancylostoma braziliense*, a common infection of dogs and cats and wild felines in many parts of the world, is rare as a human intestinal infection, but has been reported as occurring sporadically in the southern states of America, Brazil, West and East Africa, India and Ceylon, the Philippines, Fiji, and other South Pacific islands. In some places, on the bathing beaches of Florida and São Paulo, its nuisance importance in causing 'creeping eruption' is considerable

### ÆTIOLOGY

**The causal organisms.**—The two most important hookworms that parasitize man and reach the intestine are *Ancylostoma duodenale* and *Necator americanus*, the third, *Ancylostoma braziliense*, is rarer and less important as an intestinal parasite of man, but is more likely to give rise to a skin lesion known as 'creeping eruption' when it fails to penetrate the deeper layers of the skin. The three worms are morphologically similar, although readily distinguishable from one another in their adult and larval stages, their life cycles are identical, and all three produce very much the same clinical pictures when they parasitize man. The three stages of *Ancylostoma duodenale*, the egg, the larva, and the adult, will be described and any special differences exhibited by either of the other species will be noted

The eggs are colourless thin-shelled oval bodies with bluntly rounded ends, measuring on the average 40 by 80 microns. Most characteristically the protoplasm

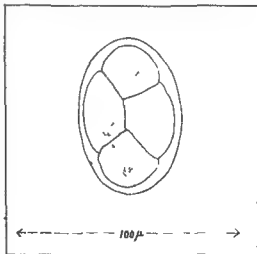


Figure 149 The egg of *Ancylostoma duodenale*

segmented stage, or with fully-developed first-stage larvae coiled within the shell. The eggs of *Necator americanus* are longer (64 to 76 microns) and narrower (36 to 40 microns) than those of *Ancylostom* otherwise similar, and the eggs are distinguishable from those of *Ancylostom*.

The larvae rarely emerge from the shell within the intestinal canal, so that when a larva is found in the stools the first assumption is that it is not a hookworm larva but one of *Strongyloides stercoralis*, however, the rhabditoid larvae of this latter species have a very short buccal cavity

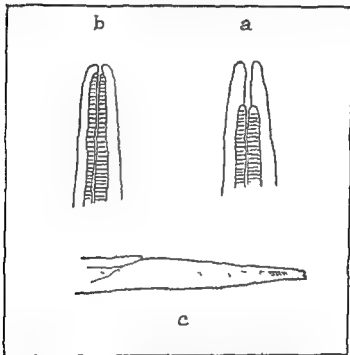


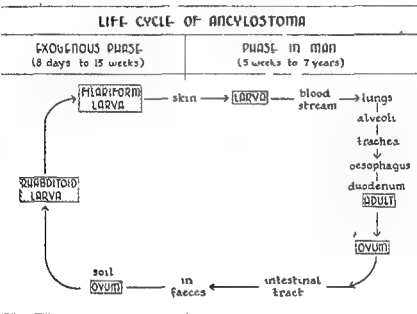
Figure 150 Showing difference between rhabditoid larvae of *Ancylostoma* (a), and of *Strongyloides* (b), and also notched tail of the filariform larva of *Strongyloides* (c) \*

(figure 150, b) which makes the hookworm larvae (figure 150, c) unmistakable on account of

The first stage rhabditoid larva, which is 250 to 300 microns long and 17 microns in diameter, usually emerges from the ovum within 24, or at longest 48 hours after the stool has been passed onto a suitable medium; here the larva feeds on organic matter for about another three days, sheds its cuticle, and becomes a second-stage larva which is about double the size of the first-stage. This larva continues to feed and grow for another three to five days and then, when it has reached about a millimetre in length, its mouth closes up and it becomes a fully-developed third-stage non feeding filariform larva. This larva sometimes retains its cuticle for a time, but sheds it before it enters its new host. When it reaches the

ejunum the larva sheds its filariform cuticle attaches itself to the intestinal mucosa feeds and grows into an adult

The adult worms are pinkish or creamy gray in colour cylindrical, lightly curved, 8 to 13 mm in length with a greatest diameter of 0.4 to 0.6 mm, the males are distinctly smaller than the females being seldom above 11 mm in length or 0.5 in diameter whereas the females are seldom less than 0.6 in diameter. The worms of the other two species are slightly smaller, *Necator americanus* varies from 7 to 9 mm by 0.3 for the male and 8 to 11 by 0.4 for the female and *Ancylostoma braziliense* is very slightly



the side of the foot, on the dorsum or between the toes, where the skin is thin and soft. They will penetrate at any other site where the skin is sufficiently thin. Laboratory workers, from Loos onwards, have frequently been infected through the hands. ■ also have miners, and bathers in contaminated waters are liable to be infected at any point on their skin surface.

The larvae can penetrate the apparently normal skin, either through the hair follicles or through microscopic faults in the epidermis, they reach the blood vessels in the dermis, and, entering a venule, they are carried in the blood stream via the right side of the heart to the lungs. In the lungs they penetrate the wall of an alveolus and migrate, via the bronchioles and the trachea, to the epiglottis, in this migration, they are aided by the ciliary epithelium of the respiratory tract. At the point of entrance into the air sac they cause a certain amount of local damage to the alveolar mucous membrane, including localized haemorrhages. At the epiglottis they pass into the oesophagus and now reversing their direction they pass into the stomach and eventually reach the jejunum, where they attach themselves to the mucous membrane and develop into male and female adult worms. Not all the larvae that start from the skin reach the jejunum, some evidently die in the tissues.

The adult worm is an avaricious and wanton blood sucker, that is, it takes far more blood than it needs for its own nutrition, literally pumping the blood out, at the rate of 0.67 c cm a day, it has been estimated in the case of *Ancylostoma duodenale*. *Necator americanus* takes less blood 0.2 to 0.5 c cm a day.

The female worm lays her eggs in the lumen of the intestinal tract, these have been variously estimated as averaging from 10 000 to 30 000 a day. The egg output of *Necator americanus* is much less and ■ usually estimated at less than 10 000 a day.

From the time the larvae enter the body to the appearance of the first eggs in the stools there is an interval of about five weeks. It has been estimated that 70 per cent of adults disappear from the intestine within a year nearly all within three years, but rare instances of persistence up to ■ years have been reported. Thus, although oviposition is believed not to be a continuous process, it is fairly certain that a single female hook-worm will produce several million eggs during her life-time. These are passed out with the faeces and the cycle begins again.

**The viability of the ova and larvae**—If the eggs do not find their way  
 \* will be slowed down or stopped  
 a long time but development is  
 estimate  
 ire  
 ire

1818 to 1900 A. J. V. C.

**Immunity**—The question of immunity in helminthic infections is not placed on an entirely satisfactory basis but there is considerable evidence that in some animals that

In dogs, the development and maintenance of immunity is dependent to a large extent on their nutrition, and when ill-nourished dogs are given an adequate diet, not only do they improve in health, but they lose their hookworms and resist further infection (Otto and Kerr, 1939)

proper nutrition of the human host

The effect of diet on the development of hookworm disease is of course well-established fact, but this is not necessarily an immunity phenomenon

susceptible to in-

This is possibly  
the skin of children,

### EPIDEMIOLOGY AND FACTORS IN HOOKWORM INFECTION

The essentials for the development of hookworm infection in a population are

- (a) The presence of one or more infected persons, as man is the only reservoir at least as far as *Ancylostoma duodenale* and *Necator americanus* are concerned
- (b) A suitable terrain around a population unit—a homestead a coolie 'line' or a village, a light soil preferably a sandy loam with decaying vegetation and shade or some other special local condition e.g. in a mine or tunnel
- (c) Promiscuous defaecation or at least a defective sanitary system
- (d) A warm humid climate (or micro-climate)
- (e) A population that is largely barefooted in the hot months of the year at least and is susceptible to infection

For the development of hookworm disease, one should add —

- (f) A sub-optimal diet for the population defective especially in iron and protein

The subject may be discussed further under each of the above six headings

(a) As has been indicated above, a single pair of worms will, during a year, give rise to several million eggs which in suitable medium will develop into a similar number of hookworms, these could theoretically cause a heavy infection in a large number of persons. In nature, however, the wastage is enormous so that to maintain a high infection rate amongst the population a rich source of infection is necessary. Other factors being equal, the infection amongst the population will vary with the degree of infection of the soil, which in turn will depend on the number of infected persons polluting the soil and the average number of ova in their stools.

(b) and (c) Four examples under which these two conditions are optimal for the development of hookworm endemicity are given

(iv) The village in India e.g., in Bengal Behar, or Assam—These villages are sometimes islands of slightly raised ground surrounded entirely by rice fields

villager defecates  
 not sun plays on  
 or larvae and at  
 buried by dung  
 has been shown  
 at least taken

further afield and there is less chance of their again coming in contact with the feet of the villagers. However when these fields are flooded, as in many places they are for several months each year, the defecating ground becomes confined to a much smaller area closer to the house, and usually more shady. Such conditions favour the larvae which remain in the locality and may a few days later re-enter the same individual's feet or infect another member of the community.

In other circumstances the advent of the rains will tend to wash out the larvae from the soil and most infections will occur in the drier season.



Figure 151 A

(iii) Tea estates in India—The tea-garden coolie is often a very primitive

Examples such as these could be multiplied indefinitely

(d) Hookworm infection is confined to hot countries, except where in cooler countries the local conditions, e.g., in a mine or tunnel, simulate those of a hot country. In subtropical countries, during the months when the night temperature falls below 50° F, larvae will seldom be found in the soil and no infections will take place during these months, e.g., in Alabama from December through March. Similarly, in hot dry countries the larvae die when the saturation deficiency rises above a certain figure, but this figure depends to some extent on the nature of the soil, in India,

Chandler (1927) found that 6 inches of rain per month was usually necessary to insure transmission of infection

In humid areas on the other hand Maplestone (1932) found evidence that the largest number of new infections were acquired in the warm months prior to the onset of the rainy season. When the rains started the ground became water logged and unsuitable for larval development

In mines infection seldom occurs if the temperature is below 70° F and conditions only become optimal in the region of 78° F

(e) Shoes or boots even if they are not defective are not a complete protection against hookworm infection. European planters in India or Indian overseers who have to walk through the highly infective mud in tea gardens although they may wear good leather boots frequently become infected but of course the infection rate is much lower than amongst the barefooted Indian labourer. The children in particular of the poor whites in the southern part of the United States usually go about barefooted at least in the summer time and in India and other eastern countries the majority of the labouring classes are always barefooted

Miners in European mines at least usually wear boots or shoes but in these the infection occurs through the hands from the soil contaminated rungs of the ladders

There is no evidence that there is such a thing in man as complete immunity to hookworm infection. Negroes are not so readily infected as white persons in the southern states of America but in India little difference in racial susceptibility has been noted. Children appear to be more susceptible than adults. There is evidence that immunity is to some extent dependent on nutrition (see Immunity p 612)

(f) Whilst immunity to infection is uncertain there is no possible question about the effect of diet on the morbidity produced by the infection. The heavier the hookworm load in comparable population groups the higher will the morbidity rate usually be but this direct correlation between the hookworm load and the degree of anaemia for example in the individuals of a group is often absent. This is probably a matter of individual differences in diet and iron assimilation. There is evidence that if the intake of iron is sufficient there will be no anaemia however heavy the hookworm load and further the writer has frequently been able to show that even in the presence of a very heavy hookworm infection it is possible to bring the haemoglobin level back to normal by iron administration alone. Similarly we (Napier and Das Gupta 1937) have shown that a high protein diet will produce a general improvement in the condition of patients suffering from hookworm disease causing the disappearance of the oedema

**Special circumstances and other factors**—Whilst the above discussion probably covers 99.9 per cent of hookworm infections there are exceptional circumstances under which infection may be acquired vicariously e.g. in the laboratory and by bathing in water heavily contaminated by fresh sewage (Ashford *et al* 1933). Dogs, pigs and jackals commonly eat human faeces. Sor but many survive so fection. Cockroaches destroys the ova and should therefore be encouraged



## PATHOLOGY AND SYMPTOMATOLOGY

**Variations in the clinical picture**—The morbidity will depend on four circumstances—(a) the species of the worm, (b) the duration of the exposure to infection, that is, whether it was a single incident (acute) or a repeated one (chronic), (c) the weight of the infection, and (d) the tolerance of the host.

(a) **Species**—*Ancylostoma braziliense*, the dog hookworm, frequently fails to reach the blood stream and so may produce only dermal lesions. Although there are some localities where this species is capable of producing the full syndrome, it is undoubtedly the least pathogenic of the three species. Between the pathogenic potentialities of the other two species, there is less difference, but *Ancylostoma duodenale* is the more pathogenic. So that the ascending order of pathogenicity is *Ancylostoma braziliense*, *Necator americanus* and *Ancylostoma duodenale*. Mixed infections are common.

(b) **Duration of exposure**—The infection is usually a more-or-less continuous or at least an oft-repeated process, but rare instances have been reported in which single heavy infections have occurred (Ashford *et al* 1933). These latter have given us a valuable glimpse of the pathological processes that probably occur in all cases but which, being as a rule spread out over so long a period, have been difficult to appreciate clinically.

(c) **Weight of infection and (d) host tolerance**—The clinical picture shows considerable variation with the weight of the worm infection and the tolerance of the host. In most areas the majority of infections are symptomless throughout, while, in others, clinically apparent infections predominate. The severity of the symptoms will, on the whole, vary in the direct ratio to the weight of the infection, but there will be many individual exceptions, due to variations in host tolerance (*vide supra*).

**Skin lesions**—At their point of entry, the filariform larvae cause a local irritation, no doubt partly on account of the organisms that they carry with them from their septic environment. As indicated above, this is usually at the sides of the foot, or on the dorsum between the toes, where the skin is soft and thin. Within about half an hour of the entry of the larva there is a burning sensation and later the area becomes intensely

irritated

and

septic organisms, so that the contents or become pustular. These vesicles or pustules, which are usually multiple coalesce and finally an eczematous patch develops. This condition is known as 'ground itch' or 'water sores', for obvious reasons.

There is some evidence that this local condition is more frequently caused by *Necator americanus* than by *Ancylostoma duodenale*, for it appears to be rare in Egypt where the latter only is found whereas in India where both worms are found, it is relatively common, especially amongst tea-estate labourers.

The pathology of 'creeping eruption' is somewhat different, as it is dependent on the fact that the larvae of *Ancylostoma braziliense* the dog hookworm is often unable to penetrate all the layers of the skin, after penetrating the epidermis, the larvae wander laterally between the epidermis and the corium in an aimless manner for a considerable time, causing a local reaction. There is local infiltration by eosinophils and

## ANCTLOSTOMIASIS AND HOOKWORM DISEASE

neutrophils with local hyperemia and edema and later vesicles along its old tracks attached off and the area. The tracks of the larva regularly twisted threads move at the rate of several centimetres in twenty four hours and duce extensive patterns throughout the skin surface of a larva survive in this intradermal locus for several weeks or even

Occasionally, the larvae of the other species cause a similar

**The larval phase**—In synchronized heavy infections (acute) evidence that some larvae do not immediately find their way to the surface of the skin, but wander in the deeper tissues taking a long time to reach the lung or perhaps never reaching it at all being placed in the tissues. In such cases acute general symptoms *e.g.* fever may simulate typhoid, and a sharp eosinophilic (75 per cent) may have occurred. It is doubtful if in the ordinary spaced infection ever any trace of this syndrome beyond a moderate increase in

**The lung lesions**—The next point at which the worm makes itself felt is in the lungs. In escaping from the lung capillary air sacs it penetrates the alveolar mucosa often causing subcutaneous extravasations of blood which may even reach the cavity of the pleura. This leads to collections of blood that are later coughed up, by the patient. Pneumonitis has been reported but is rarer than in the cases of *Strongyloides* infections. In cases in which there is an acute and heavy synchronized infection there may be a sensation of constriction in the throat with difficulty in swallowing.

**Gastro-intestinal symptoms**—In the acute case, discomfort and discomfort is a common symptom it often persists and may be evidence of the infection. In heavier infections that have been present over a long period especially in poorer class Indians and other populations these gastro-intestinal symptoms stand out from the picture of ill health. The diarrhoea may be due to the local irritation and the absorption of metabolites in the intestine, but Ashford and his coworkers (1935) believe that it may be the result of helmintholysis from the live or dead larvae that have gone astray in the intestine (*vide supra*).

In the acute case, if there is no further infection, the acute symptoms will tend to subside as the adult worms settle in the jejunum, but if the infection has been repeated and the worms are not removed

**General symptoms in established (chronic) ancylostomiasis**—When the adult worms are established in the jejunum they suck blood, possibly inject some 'toxin', and make small lesions in the mucosa which may allow septic absorption. The recognized syndrome of ancylostomiasis will now develop.

The fully-developed ancylostomiasis syndrome shows a patient with oedema of the extremities and face—the puffy pale ancylostomiasis facies—mucous membranes almost white, hair scanty, and a protuberant abdomen. The patient has a vacant expression, he has no energy and is indifferent to his surroundings. He complains of palpitations and is breathless on exertion. He suffers from dimness of vision and night-blindness. Examination shows that his heart (both right and left side) is extremely dilated; there is usually a mitral systolic murmur and sometimes one at the pulmonary base, his pulse is rapid, and his blood pressure low. His tongue has a wash-leather appearance and often a black streak down the centre. A watery diarrhoea is common.

The cardiac changes, which are all secondary, to severe endocardial damage that is in turn caused mainly by the anaemia, are easily reversible when the blood picture is improved by anti-anaemic treatment alone, but there are a few cases in which this improvement will be delayed until the worms are expelled, thus suggesting a possible second factor of a toxic or an allergic nature (Heilig, 1942).

Patients will usually have taken several years to reach this miserable state and in the case of children their physical and mental development will have been retarded, so that a child of 16 years of age may physically and mentally appear to be no older than 10 years, and at the same time he will lack the childish energy and desire to play with other children. Sexual maturation is also retarded. A curious craving manifested by geophagy (or eating of earth), often develops.

The anaemia is perhaps the most striking morbid change and it is certainly the most easily measured so that the blood picture will be discussed in some detail.

**Blood picture**—*The cause of the anaemia*—Until a few years ago there was much difference in opinion on the actual cause of hookworm anaemia. It is now well established that it is a true secondary anaemia due to the sucking of large quantities of blood from the lumen of the intestinal canal. The lost blood is replaced by the absorption of iron and other substances, but this is done at the expense of the reserves of iron and other substances. Even with a heavy load of worms anaemia can be prevented or even cured by giving the patient a good protein diet plus medicinal iron, but in persons living on the borderline of iron starvation anaemia will be caused by quite a moderate load.

While most cases can be cured by iron administration alone (*vide infra*) there are a few exceptions in which the normal blood level cannot be regained without the removal of the worms. It has been suggested that the worms may also introduce some toxin or allergen. However, in a small series of examinations and sternal puncture (Majumdar, 1941) failed to see any evidence of the repressive effect on the bone marrow of the hypothetical toxin and we suggested that these few exceptions might be the result of malabsorption of some essential blood-

forming element as a result of course, of dysfunction caused by the hookworm infection

*The nature of the anaemia*—A more striking reduction in haemoglobin can occur in hookworm disease than in any other disease of equal seriousness. The writer has seen tea estate coolies walking into the dispensary with a haemoglobin percentage that was estimated by the tea estate doctor as 5 per cent on the Tallqvist scale. The blood that came out when one pricked the finger of such patients was a thin watery fluid which would not make a proper smear even on a scrupulously clean slide. The colour was in fact, well below the 10 per cent matching on the Tallqvist scale and by more accurate methods a figure of 1.5 grammes of haemoglobin per 100 ccm of blood was not an unusual finding with 900 000 red cells per cmm and a packed cell volume of 6 per cent: this gives a mean corpuscular haemoglobin of 10.7 cu  $\mu$  and a mean corpuscular volume of 107 cu  $\mu$  and a nearly always not usually

There are usually a few normoblasts present and 2 to 5 per cent of reticulocytes: the van den Bergh reaction is negative

There is often an increase in blood volume: this compensates to some extent for the extreme anaemia and possibly explains why patients can live and even work with such low percentages of haemoglobin. There is a decrease in the serum proteins and in both calcium and cholesterol

*The white cell count*—The total count is usually between 5 000 and 10 000 per cmm. That is more or less normal but the eosinophil percentage is usually raised. An average count of 14 per cent is not unusual but in the very heavy infections the count is often within normal limits or eosinophils may even be absent

*Gastric acidity*—There are conflicting statements in the literature on this subject. We found in a series of 28 Indians that the gastric acidity was normal or increased in 21 (or 75 per cent) and that the relation be-

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possibly an independent contributory factor in the cause of anaemia. There were in this series only three cases of complete achlorhydria. Anti-anæmic treatment causes no striking improvement in the acidity

*Fæces*—The stools are watery. As well as the ova which will be discussed below, there is nearly always occult blood

## DIAGNOSIS

*In the parenteral phases*—The diagnosis of the 'ground itch' would be difficult without the epidemiological background and the condition is likely to be confused with the secondary pyogenic infections in tinea infections and of other skin conditions but 'creeping eruption' produces a map-like effect on the skin that is very characteristic. *Gnathostoma* sp. produce to ca only

or the fly-maggot from the lesions. There is little opportunity to make an accurate diagnosis at any other stage of the parenteral infection, although in a few cases larvæ have been coughed up from the lung.

**In the intestinal phase**—The clinical picture of hookworm disease is a characteristic one and so also is the anæmia (*vide supra*), but it would not be justifiable to make a diagnosis without the confirmation of stool examination. The finding of hookworm ova in the stools is evidence of *hookworm infection*, but, even when the ova occur in relatively large numbers and the patient is anæmic, this is not necessarily evidence of *hookworm disease*, as the anæmia may have some other cause. Many populations have an infection rate of almost a hundred per cent without much morbidity directly due to the worms, and great care must be taken to view these hookworm infections in their proper perspective and not attribute either too much or too little to them. In the early days several experienced investigators made serious mistakes in this direction (*e.g.* Giles in Assam attributed kala-azar to hookworm infection). In the absence of other obvious causes of illness, and on the finding of perhaps a single egg, it is often tempting to label a patient 'ancylostomiasis', but this should not be done without a very thorough investigation to exclude other causes. On the other hand, in some groups, in Europeans in India for instance, mild but troublesome gastric-intestinal discomfort, and they should

not be ignored.

**Examination for ova**—It will be possible to make a diagnosis in any clinically significant infection, and even a rough estimate of the hookworm load by a direct examination of a stool emulsion under the microscope, but for recognizing very light (initial or residual) infections for example in testing the efficacy of a drug, concentration (*e.g.* floatation) methods should be used.

#### Technique

1. Place a small amount of stool on a large microscope slide and mix with a thin emulsion of

2. Allow to stand for 10 minutes and then place a coverglass over the mixture.

In the absence of a centrifuge the zinc sulphate solution can be added directly to the faeces mixed thoroughly and allowed to stand for a few minutes after which the floating ova are collected on a coverglass in the way described above.

Lane's direct centrifugal floatation method which entails the employment of a special apparatus is dependent on the same principle. It is possibly the best method

for finding the last egg in a stool but the former of the methods described above falls very little short of Lane's method and is sufficiently accurate for all practical purposes

**Estimating the hookworm load**—The methods for doing this *before* treatment are necessarily rough, but it is generally considered that one female worm will pass enough eggs to represent 80 eggs per gramme of stool, and on the assumption that the sexes are equally divided, this means that each 40 eggs per gramme represents one worm

We have adopted the principle of grouping hookworm loads as follows—

I Light load	= under 2000 eggs per gramme
II Moderate load	= over 2000 but under 10 000 eggs per gramme
III Heavy load	= over 10 000 but under 40 000 eggs per gramme
IV Very heavy load	= over 40 000 eggs per gramme

The last figure is equivalent to a load of 1,000 worms

*After* treatment the worms can be counted by collecting all the stools for 48 hours and washing them through a fine (1-mm mesh) copper sieve. The adult worms will be held back by the sieve and can be counted

There are several methods for estimating the number of ova but the following modification of the original Stoll method is in the writer's experience the best—

**Technique**—A test tube of suitable size is marked at the 27 cm and the 30 cm levels. Decinormal sodium hydroxide is poured into the tube up to the 27 cm level and portions of stool added until the fluid reaches the 30 cm level. The

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**Other diagnostic aids**—Instances have been reported in which, though no ova were found in the stools, adult worms were found post mortem. The usual explanation is that these have all been male worms. If this state of affairs is suspected, the therapeutic test and careful examination of the stools for adult worms should clear up the point

The finding of an eosinophilia will naturally lead to a suspicion of some helminth infection, but will be of no real diagnostic value, further, when the infection is a heavy one and the morbidity considerable, there will usually be no eosinophilia

Tr. 21.

delayed for any reason the ova may  
will have to be differentiated from  
the most striking point of difference  
latter. In extreme cases *filariiform*

larvæ may develop, but the differentiation of these from the *filariiform* larvæ of *Strongyloides* presents little difficulty as the latter have a notched tail that is quite characteristic

## PREVENTION

**Introduction**—It will first be necessary to make an accurate assessment of the problem to be faced. This will require a clinical survey of representative groups of the population, including at least some rough estima-

tion of hemoglobin an examination of the stools preferably of the same

passing (see p 621) than by working out an average for the whole number examined—and finally, if possible an estimation of the infectivity of the soil\* in areas where most infections are thought to occur, this last investigation should be made at several different times of the year. These examinations will have to be repeated periodically to measure the success or failure of the procedure. (For short descriptions of the methods of stool examination see p 620.)

In order to obtain a view of the subject of prevention in proper perspective it should be considered under two headings namely, (I) the prevention of hookworm infection and (II) the prevention of hookworm disease, despite the fact that there will be much overlapping in the two aims.

(I) **Prevention of infection**—The reader is asked to turn back to p 613 where the five essentials for hookworm infection are given we will consider the subject under each of these five headings.

(a) Man is the sole reservoir of infection of the two important species so that effective anthelmintic treatment will have the double result of curing the individual and reducing the source of infection in the community.

(b) The circumstances are such that it is seldom that anything can be done to improve the terrain, but where the area is a very limited one as in mines attempts have been made to reduce its suitability as a medium of infection by treatment with such substances as common salt.

(c) The proper disposal of human feces by installation of sanitary latrines and the encouragement—or the enforcement—of their use by the whole population is the crux of the whole hookworm problem, and where this is possible all other preventive measures become subsidiary. This is

all naturally vary with the conditions. The red hole latrine has been a very successful one. One of the main objections of this system obviates the prejudicial effect of the communal latrine. It is of the

utmost importance that any scheme that is introduced should be easily workable and suited to the special circumstances; it must not be liable to break down as an unsatisfactory latrine will do more harm than good. This aspect of prevention is so important that it must always be remembered.

\* **Estimation of larvae in soil**—This is most easily accomplished by the Baermann technique which depends on the fact that larvae will migrate out of soil into warm water that comes in contact with the lower surface of this soil. The technique is described by Craig and Faust (1913) as follows:—

The simple apparatus used consists of a glass filter funnel of 15 to 23 cm,

sediment poured on to a slide for examination. The examiner needs skill and experience to differentiate hookworm and *Strogylodes* larvae from nematodes free living in the soil.

bered that, whatever other measures are taken, the only enduring solution will be proper disposal of human excreta, the source of infection, and a beginning must be made to this end

Education and propaganda will play an important part in the prevention scheme, as not only has understanding to be imparted, interest aroused and ingrained habit broken, but quite often active prejudice has to be overcome

Where human excreta is used for manure, either septic tank treatment for a considerable time, at least 3 months in a temperate climate, or six weeks in a tropical one, or some other means of 'sterilization' must be employed, e.g. the addition of lime to a dilution of 1 in 500 or mixture with litter to make a form of compost and burial in the earth which will raise the temperature sufficiently to destroy the eggs and larvae. But this particular problem is a difficult one and has not yet been satisfactorily solved

(d) Climatic conditions are matters outside human control

(e) The wearing of good boots or shoes will decrease the chance of infection but not stop it completely. Unless this is an entirely foreign custom amongst the people, the wearing of boots or shoes should be urged. Propaganda will again find an important place here

**II Prevention of hookworm disease.**—It is again necessary to recapitulate. Certain facts must be remembered

(i) Hookworms do not undergo any multiplication within the body of the host so that without re-infection there will be no increase in their number but in fact a relatively rapid reduction (placed at 70 per cent in the first year by some observers) will occur. If the infection is not to die out it will have to be repeatedly replenished. We thus have the equation

$$\text{hookworm load} = \frac{\text{the rate of acquisition of infection}}{\text{the rate of worm loss}}$$

(ii) The hookworm load at any particular moment will vary from one worm to several thousand and similarly the infection may be either sub-clinical or symptomatic however the relation between these two facts is not a simple and direct one but morbidity is dependent also on the tolerance of the host or in other words

$$\text{morbidity} = \frac{\text{hookworm load}}{\text{host tolerance}}$$

(iii) Host tolerance is dependent on certain fixed factors such as age and race, but it is also influenced considerably by a variable factor the diet of the host

The eventual aim of prevention is the reduction of hookworm morbidity in the population. It will be seen from the above equations that this can be done by

- (a) reducing the hookworm load or
- (b) increasing the tolerance of the hosts

The hookworm load can be reduced by

- (c) decreasing the rate of acquisition of infection or
- (d) increasing the rate of worm loss

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The only practicable measure for achieving (b) increase in tolerance, is also by dietary improvement

\* Referring to the number of worms that actually reach the bowel



Thus to summarize hookworm morbidity can be reduced by —

- (i) Improvement in environmental hygiene (*sensu lato*)
- (ii) Anthelmintic treatment
- (iii) Improvement in diet

It must be quite obvious that if the rate of the acquisition of infection is sufficiently decreased by sanitary improvement or the rate of worm loss is sufficiently increased by mass treatment or both effects are brought line and the average the morbidity level ed this end will be achieved at an earlier date. In this way the morbidity in the population may be reduced without achieving the ideal of a perfect sanitary system which in most cases will be impossible or the complete deworming of the community which in most cases will be impracticable. The great disadvantage of this method of approach is that continued vigilance to ensure that there is no dangerous increase in the hookworm infection in the population and usually periodic retreatment will be necessary.

**Policy**—There have been two realistic schools of thought demanded lines indicated in the last section of this morbidity in that the aim should be the reduction of this being measured in terms of the number of infected persons left in the population.

We will consider the latter first. It is impossible to criticize the ideal but how far is the aim practicable? To achieve complete success not only the symptomatic cases but every member of the population who shows any hookworm infection must be treated (if he will consent). To ensure the removal of all the worms even by the most efficient method at least three treatments will be required in a large number of cases and an elaborate method of stool examination will be necessary to check the results. Further this whole process will usually have to be repeated at monthly intervals for a period of four months to catch all the fresh worms—those migrating in the tissues and those acquired from larvae surviving in the soil since the first mass treatment—before they can produce any eggs. Even then a few worms may escape and should complete success be achieved a casual

success would be so improbable that it would be scarcely worth attempting.

The policy of the realistic school is the one now generally adopted. Complete treatment of the whole community is not usually attempted but treatment is concentrated on the members of the families or of the habitation groups in which any cases of hookworm disease are found. One course of anthelmintic treatment is given to each member and medical treatment for the anaemia plus a second course of anthelmintics if necessary to those with clinical evidence of the disease. The most favourable time for giving such a course of treatment is during the period—when there is one—in which transmission does not occur *e.g.* in the southern states of America the temperature prevents transmission between November and March.

By this modification of the mass treatment programme much time-consuming laboratory work is saved and the number of treatments given is

reduced very considerably although it may be advisable to repeat the treatment every few years. It has been found that if this procedure is combined with the provision of latrines and the dissemination of propaganda regarding their proper use a steady decline in morbidity will take place year by year.

In conclusion, it must be remembered that none of these measures mentioned above can be put into effective operation without explaining to the people the cause of the disease and the necessity for their whole hearted cooperation so that to the measures summarized on p. 624 must be added

(iv) Education and propaganda

# TREATMENT

This must be considered under the two major headings (I) treatment of the parenteral infection and (II) treatment of the intestinal infection and the latter can be divided into (a) specific treatment and (b) general treatment

I The parenteral infection—Except that in the case of creeping

## II Intestinal infection—(a) Specific

Historical—Prior to about 1917 chloroform, beta naphthol and thymol were the principal drugs used of these thymol was undoubtedly the best. A dose of

drugs have since been introduced it only deserves mention in an historical section

Chloroform and oil of eucalyptus was the standard treatment for this and other helminth infections in the early days of the century and deserves honourable mention whereas beta naphthol is quite useless in safe doses and it is difficult to see why it was ever advocated

chloride or tetrachlorethylene but given a one for hookworm infection its effective dose (3 c cm for adults) is dangerously near its toxic dose so that it has been superseded except for mixed infections

In 1922 Leach used carbon tetrachloride in man a drug that had been used successfully in dogs by Hall and it was later used in hundreds of thousands of

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used. It appeared too late to be used in treatment campaigns so that it was slow in use. However, it has now been used in very few ill effects and no fatalities have been reported. A single treatment may be expected to remove 99 per cent of *Necator americanus* and 96 per cent of *Ancylostoma duodenale*.

**Tetrachlorethylene (C<sub>2</sub>Cl<sub>4</sub>)** is undoubtedly the drug of choice. It is best given in the form of a suspension in saturated sodium sulphate, 4 c cm of tetrachlorethylene is shaken vigorously in a stoppered bottle containing two ounces of saturated solution of sodium sulphate and then taken by the patient before it has time to settle.

The dose for children is 0.2 c cm for each year of age. The drug should be taken early in the day on an empty stomach. Some workers advocate water the night before to avoid difficulties about

The only ill-effects are a slight sensation of giddiness and in some cases exhilaration as occurs after taking alcohol. The treatment may be repeated in a week's time if necessary.

If there is a mixed ascariis and hookworm infection, oil of chenopodium, 1 c cm, should be added to the tetrachlorethylene under the same routine.

**Hexylresorcinol** (1,3-dihydroxy-4-hexylbenzol), although slightly less efficacious than tetrachlorethylene, has a special use in seriously debilitated patients. It is the least toxic of the anthelmintics in general use, it is given in one gramme doses, in five hard gelatin capsules containing 0.2 gramme each. The dose for children under 6 years is three capsules (0.6 g) and for older children 4 capsules (0.8 g). The capsules, which must be swallowed and not bitten or a local irritation will be caused, are taken on

**Checking results of treatment**—If this is to be done accurately the stools must be screened for dead worms (*vide supra*), but for mass treatment it will seldom be possible to do anything more than examine the stools for ova. This should be postponed until about the seventh day after treatment, as otherwise eggs passed by worms before the treatment was given may be encountered and vitiate conclusions. If there are still more than 200 eggs per gramme, the treatment should be repeated.

(b) **General**—Malnutrition is a common accompaniment of hookworm infection and whenever possible a general dietary improvement should be instituted. An increase in the intake of both iron and protein is particularly indicated, however, the improvement in the anaemia need not be unnecessarily delayed by relying on dietary iron but medicinal iron should be given whenever necessary. It has repeatedly been shown that will effect little if any (152), but on the other it is possible to bring the blood level up to normal by iron administration alone and in very on prior to the administration of a second course of

Iron can be given conveniently in the form of ferrous sulphate tablets, grs vi, three times a day for 21 days a total dose of 378 grains, or better

still in a mixture. For the mixture, 12 grains of ferrous ammonium sulphate ( $\text{Fe SO}_4 (\text{NH}_4)_2 \text{SO}_4 6\text{H}_2\text{O}$ ), in half an ounce of dextrose, is taken three times a day for 21 days. The iron content of the mixture is a little less than that of the tablets, even though the dose of the salt is doubled but none the less the response to the mixture is usually more rapid. Two

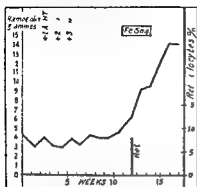


Figure 152 Showing absence of effect on hæmoglobin level of three doses of 3 ccm of  $\text{CaCl}_2$  + 1 ccm oil of cadopodium within a period of 8 weeks and immediate effect 18 grains of ferrous sulphate daily

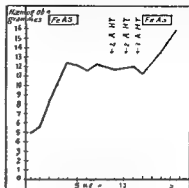


Figure 153 Showing the immediate effect of 18 grains of ferrous ammonium sulphate daily before deworming

21-day courses of iron are usually sufficient to bring the hæmoglobin to normal even in the most severely anæmic cases the result of treatment should be checked by blood examination

The writer questions whether it is ever necessary or even advantageous to give a blood transfusion in an ordinary case of hookworm infection however severe the anæmia, in view of the extremely rapid response to iron that can be expected, but in the special case, e.g. of the pregnant woman who is nearing full-term, this will perhaps be indicated

### PROGNOSIS

From the public health point of view the chances of ridding a population of hookworm infection will depend on how much sanitation it will be possible to install, if money is the limiting factor or on how much the population can be induced to take advantage of the sanitary conveniences installed, if ignorance and custom, religious or otherwise, are the main handicaps against which one has to work. In most countries where a de-  
rove sanitation the hookworm posi-  
tion five or six years where this has  
ugns, very appreciable improvement

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medicinal iron are given, even the most anæmic patient may be restored to good health within as short a time as a month

Unless the patient is first seen in *extremis* death should never occur in an uncomplicated case of *ancylostomiasis*, but in the very anæmic patient treatment for the anæmia should be given first.

The pregnant woman, however, with severe *ancylostomiasis* often fails to survive parturition. On the other hand, if the anæmia is solely due to the *ancylostome* infection and is therefore an iron deficiency anæmia, the chances of survival of that inexorable parasite, the foetus, who appropriates all the iron it requires, are good (Napier and Edwards, 1941).

## STRONGYLOIDIASIS

**Introduction.**—It may be said of this infection that clinicians tend to pay it too little and helminthologists too much attention in proportion to the pathogenic proclivities of the parasite and the extent of its incidence. The explanation for the attitude of the latter is not difficult; this worm has a complicated and variable life cycle, unique in helminthic infections, that includes an extensive sojourn in the human tissues that might reasonably be expected to call forth considerable tissue reaction. On the other hand, there is little doubt that while serious infections are common enough to make the dismissal 'pathogenicity doubtful' of some textbooks quite unjustifiable, the total amount of morbidity and mortality that this worm produces, directly or indirectly, throughout the world, is infinitesimal compared with that caused by the hookworm.

**Geographical distribution.**—This is world-wide, but mainly tropical, and the infection is particularly associated with the more humid tropical areas. It is obviously far more common in the southern states of North America and in South America than in the tropical areas of the eastern hemisphere (Faust, 1936). It is relatively uncommon in China and in India, although in the latter the writer has seen a number of instances of this infection in which there was some degree of associated morbidity.

## EPIDEMIOLOGY

The conditions which favour this infection are roughly those which favour in the intensity endemic areas certain differences allelism in the merent parts of the

There is a distinct male predominance amongst the persons infected, and the age groups with the heaviest infection rates are in the second decade.

The incidence is often high in institutions, such as mental hospitals.

## ÆTIOLOGY

**The causal organism.**—The stages through which the worm passes are as follows.

**The egg.**—This is fully embryonated on discharge from the uterus, it is deposited in the tissues in the parasitic phase and is seldom seen except in experimental infections. It has a thin transparent shell, is ovoid in shape, and measures about 54 by 32 microns.

**The rhabditoid larva.**—This develops from the egg in the tissues, reaches the lumen of the gut, and is passed, usually as such, in the faeces.

It is about 250 microns in length and can be distinguished from the hook-worm larva by its shallow buccal cavity (figure 150, b)

**The filariform larva**—This develops from the rhabditiform larva usually outside the body, but also in other instances within the intestinal canal. It is a long (about 1 mm) fine larva with a long oesophagus and a distinctly notched tail (figure 150, c). Occasionally, dwarf filariform larvae develop from the rhabditoid larvae in the intestinal canal.

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**The life cycles**—The filariform larva is the infective stage. The larvae enter the skin of man in the same way as the *ancylostoma* larvae, but

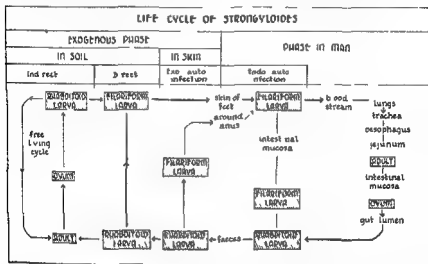


Figure 154

also through the buccal or pharyngeal mucous membrane, reach the lungs via the blood stream, and penetrate into the alveoli. They may develop into adults here, but otherwise they ascend via the bronchi and trachea to the lungs. The whole journey takes about a month. These larvae feed on organic matter in the soil.

One of two things will now happen

If the larvae find themselves in a sub-optimal medium, they develop into non-feeding filariform larvae which are the infecting forms, they enter another host, and the direct parasite cycle is complete.

Or, if conditions are optimal, then the rhabditoid larvæ feed, pass through one moult, feed again, and develop into free-living adults, these mate, the female lays eggs which develop into rhabditoid larvæ in the soil, and the free-living cycle is repeated, probably an infinite number of times as long as conditions remain favourable, but, when they cease to be so, the rhabditoid larvæ develop into filariform larvæ, which, though they will survive as such in the soil for many months, are immediately infective and capable of entering another human host to complete the indirect parasitic cycle

larvæ may not go back to the soil, but may continue to live on to the soil around the anus, and re-enter the skin. The former of these last two cycles is called by him 'auto-infection', and the latter 'hyperinfection'.

Our parasitic cycles, (a) endo-auto-infection (Faust's hyperinfection), (b) exo-auto-infection (Fulleborn's auto-infection), (c) direct (comparable to that of the hookworm), and (d) indirect in which the free-living cycle is interposed (see figure 154)

**Discussion.**—The practical significance of the auto-infection cycles is that an individual can apparently retain the infection almost indefinitely without renewing it from outside. The auto-infection cycles are nowhere common but are more important in temperate climates where both conditions for the survival and opportunities for the re-entry of the parasite are more favourable than in tropical climates. Another point is that oral infection is apparent, and infection can be initiated through the skin of the feet or hands.

**Contributory factors in determining morbidity.**—There is considerable evidence that diet is a very important factor in determining pathological changes in the host. In disease, the host is deeply affected.

#### PATHOLOGY AND SYMPTOMATOLOGY

As in the case of hookworm infection, this worm produces pathogenic lesions commonly at three points on its course, (a) in the skin at the point of entry, (b) in the lungs, and (c) in the intestinal mucosa, and rarely in the bronchi and trachea.

\* The word 'hyperinfection' seems a most unfortunate choice for this cycle. The word is well established in medical language as meaning 'a very intense infection'. This cycle is certainly auto-infection, but if it is desirable to differentiate it from Fulleborn's auto-infection—and from a practical point of view it is questionable whether it is necessary—then the words 'exo-auto-infection' might be used for the Fulleborn cycle and 'endo auto-infection' for the Faust cycle.

(a) **The skin**—Here the filariform larvæ may produce petechial hæmorrhages at their points of entry. The site later becomes very irritating and there may be a localized œdema.

(b) **The respiratory tract**—Hæmorrhages may be caused in the lung and these may be associated with a cellular exudate into the alveoli. This frequently causes a cough during which blood stained sputum containing larvæ may be brought up and after heavy infections an atypical pneumonia may occur. Occasionally the worms mature in the lungs and invade the columnar epithelium of the bronchi and trachea causing a local exudate. The respiratory lesions and symptoms are likely to be greater in this infection than in ancylostomiasis.

(c) **The intestinal tract**—The adult females invade the mucosa as deep as the muscularis mucosæ and cause desquamation and occasionally sloughing of the mucous membrane with abdominal discomfort or pain sometimes a frank dysentery but more usually a profuse watery diarrhœa or diarrhœa alternating with constipation, loss of weight and indigestion. The infection is often associated with insomnia, restlessness and depression.

**The blood picture**—There is usually a slight leucocytosis with an 8 to 10 per cent eosinophilia at first and later a leucopenia. There may be some slight degree of anæmia usually of the macrocytic nutritional type.

#### DIAGNOSIS

This can be made by finding the larvæ in the stools. Concentration of the stool will facilitate this. The larvæ appear in the stools intermittently and therefore no importance should be attached to a single or even several negative findings. Further the larvæ may die and be digested during their relatively long journey down the intestinal canal thus in a case in which the infection is strongly suspected some workers recommend that a duodenal aspiration should be done. Or the larvæ may be coughed up in the sputum.

The larvæ must be differentiated from the hookworm larvæ the main point of difference is the shallow buccal cavity in the strongyloides rhabditoid larva and the notched tail in the filariform larva (*vide supra*).

#### PREVENTION

The main measures to be adopted are those employed against hookworm infection (*quod vide*). In addition the existence of this infection in a community necessitates the following measures:—  
 1. Improvement in sanitation.  
 2. Care in the preparation of drinking water supplies.

Improvement in the diet of an infected population or individual will help to prevent the more serious results of infection.

#### TREATMENT

This has been very disappointing as none of the anthelmintics that have been so successful in the treatment of ancylostomiasis have proved of any value in this infection. Gentian violet is considered the only specific but this has not been successful in the hands of all workers in some cases this was possibly because they did not adopt the right technique but there is evidence of a variable resistance to treatment. Experiments have shown that this drug will penetrate at least as far as the muscularis mucosæ.



# TAPEWORM INFECTIONS

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**Introduction**—There are three important large intestinal tapeworms that infect man, namely

*Tænia saginata* Goeze, 1782, the beef tapeworm

*Tænia solium* Linnæus, 1758, the pig tapeworm, and

*Diphyllobothrium latum* (Linnaeus 1758) Iube 1910 the fish tape worm

and two dwarf tapeworms

*Hymenolepis nana* (v Siebold 1852) Blanchard 1891

*Hymenolepis diminuta* (Rudolph 1819) Blanchard 1891

## LARGE TAPEWORMS

None of these infections is tropical in its end for their distribution upon the various countries and, as the control of countries the meat-eating sojourner infection with either the pig or the beef tapeworm in a tropical country than in the United States or in any of the western European countries. In eastern Europe the pig tapeworm especially is relatively common.

The fish tapeworm on the other hand is rare in the tropics, and occurs in the Baltic countries northern Italy and Switzerland in the Danube delta, in Palestine in Siberia Manchuria and Japan in some places in the northern states of America and in Canada and sporadically elsewhere. In the last named countries the foci of infection are mostly on the shores of the great lakes where the infection was probably introduced by Scandinavian immigrants but recently a focus has been found in Florida.

### ETIOLOGY

The parasites — The tapeworms are flat hermaphroditic worms consisting of — (i) a scolex the so called head which is an attachment organ (ii) the neck which is narrow and formed by a number of undifferentiated proglottids (iii) a short section of differentiated but immature proglottids or segments in which the male and female sex organs are present (iv) a long section of mature proglottids and finally (v) the gravid proglottids. These worms have no digestive tracts but absorb nutrition from their environment in the gastro-intestinal tract of their hosts. The life cycles of the different species vary so much that it will be necessary to describe them separately.

### Life Cycles

*Tania saginata* — Man is the only important definitive host he passes the proglottids in his faeces and, when these disintegrate, the ova, which are

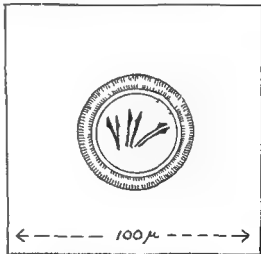


Figure 156 The egg of *Tania saginata* that of *T. solium* is identical

spherical, 30 to 40 microns in diameter, have a thick shell and contain an onchosphere with three pairs of hooks, are set free. These are ingested by cattle, in whose gut (duodenum) onchospheres emerge and penetrate the bowel mucous membrane, reach the systemic circulation and are filtered out in the muscles. Here they develop into cysticerci in about 60 days. These cysticerci which are white oval bodies 7 to 10 by 4 to 6 mm are the infective form for man who ingests them in raw or under-cooked meat. From the cysticerci the worm develops, attaches itself to the small intestinal mucosa, and proceeds to grow into a mature worm, measuring from 4 to 10 metres with as many as 2 000 segments, in about three months. Gravid proglottids now begin to drop off one by one, pass out of the anal orifice under their own power or in the faeces, and the cycle is complete.

*Tænia solium*—The cycle of this tapeworm is similar to the above, with the pig replacing cattle as the usual intermediate host. However,

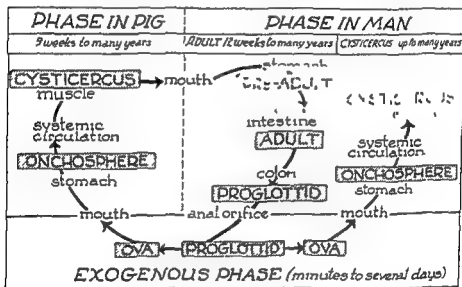


Figure 157 The life cycle of *Tænia solium*. (The possible endo auto-infection is not shown in this diagram.)

that man may also function as a host, from another host, of his own adult worm, or by endo-auto-infection brought about by reverse peristalsis, so that the proglottids or eggs reach the stomach where the covering is digested off and the eggs are released and reach the almost

*Diphyllobothrium latum*—There are many definitive hosts of this worm other than man—the domestic pig, the domestic dog and cat and other canines and felines, walruses, seals, sea-hions, minks and bears. The eggs, which are golden-brown in colour, ovoid, 45 by 70 microns contain immature larvæ within a thin shell, and have an opening at one pole covered by a cap, are passed in the faeces (figure 158). In water these mature within fifteen days and the embryos (coracidia) emerge, these are

ciliated and swim freely in the water up to 12 hours, after which they would die if they were not ingested by a copepod (crustacean) of certain species of the genera *Diaptomus* and *Cyclops*. They develop in these for two to three weeks and when the crustacean is swallowed by fish these embryos develop into plerocercoid larvæ, long white larvæ measuring up to 6 millimetres, in the flesh (muscle) of the fish. The small fish that eat the crustaceans are later eaten by larger fish such as pike, perch, trout and other fish commonly eaten by man (and other definitive hosts), and in the human intestine these larvæ develop into adult tapeworms in about six weeks. This species grows to a length 10 metres or more, and may have as many as 3000 proglottids. The eggs are evacuated into the intestinal canal from the mature proglottids, which do not separate as in the case of the other tapeworms but atrophy after they have discharged their full egg load. These worms may produce as many as a million eggs a day, but they usually evacuate their eggs periodically, about every third day, for about a month. The eggs are passed out with the faeces and the cycle is complete.

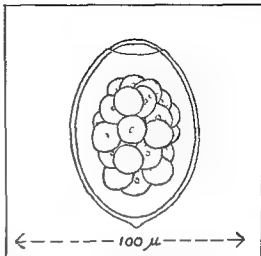


Figure 158 The egg of *Diphyllobothrium latum*

#### EPIDEMIOLOGY

These infections occur amongst meat-eating and fish-eating persons in many countries but are particularly common amongst groups who eat their food raw or only lightly cooked and in countries where pigs have easy access to human faeces which they will readily eat, or cattle graze in pastures which are frequently contaminated by or deliberately manured with, human excreta.

A number of cysticercus infections in British soldiers who have been stationed in India have been reported.

The fish tapeworm infection appears to be extending in the United States, several fresh endemic foci have been identified and infected fish are sometimes sent to market in distant towns.

#### PATHOLOGY AND SYMPTOMATOLOGY

In none of these infections do the adult worms or the excysted larvæ ordinarily invade the host's tissues, but they deflect a certain amount of the host's nutriment to their own use, and secrete substances which may

act as toxins or allergins. Rare instances of the scolices having penetrated the intestinal wall and caused peritonitis have been reported. And finally the cysticerci of *T. solium* may develop in man, as they do in the usual intermediate host in any tissue or organ of the body. As the pathogenesis and symptoms produced by each of the two stages of the worm are of an entirely different order from those produced by the other, it will be advisable to describe them separately.

**The adult worms**—The symptoms produced are irregular and ill defined. Loss of weight indigestion and general abdominal discomfort and in allergic individuals periodic diarrhoea may occur. All somatic symptoms may be absent, especially in *T. saginata* infection but the host may be reduced to a state of neurasthenia by knowledge of the presence of the worm, and by the embarrassment caused by the emerging segments which may appear at unexpected moments on the host's stockings or shoes. In *D. latum* infection, however, there is in certain cases evidence of some intoxication produced by the metabolites of the worm. A macrocytic anaemia of the pernicious anaemia type has for many decades been associated with this infection. Although the work of Birkeland (1932) seemed to cast doubts on the causal relationship between the infection and the pernicious anaemia that is very prevalent among Finnish nationals more recent work seems to support the suggestion that the worms' metabolites which are of the nature of unsaturated fatty acids are capable of producing anaemia (Wardle and Green 1941). Anaemia has not been reported in Canadian and North American cases.

**The cysticerci of *T. solium***—The oncospheres having reached the blood stream migrate into the tissues in any part of the body, but appear to have a preference for the brain, the muscles and the subcutaneous tissues. Here they give rise to a tissue reaction and are eventually surrounded by a fibrous capsule of host origin. Within this rigid host capsule the cysticercus continues to develop the parasitic wall of the cyst becomes folded upon itself and in some cases produces a relatively large 0.5 to 1 centimetre racemose cystic growth. There is apparently a stage at which a balance between host and parasite is reached and no further development takes place for several years, but, when the parasite dies this symbiosis is disturbed the capsule becomes permeable and fluid enters and toxin escapes so that there is renewed tissue reaction and an increase in the size of the parasitic mass at least temporarily. Later, there is either calcification or the foreign body is partly or completely removed. The life of the cysticercus is probably very variable but it is probable that they live for at least three years and after their death at least another three years elapses before they become calcified.

The symptoms depend on the site in which the cysticerci are located and of course on the number present. A heavy invasion may be associated with pyrexia other general symptoms of a toxæmic nature and pressure symptoms if vital tissue is involved. Generally however the symptoms are postponed until the worm dies when further pressure and toxæmic symptoms may appear. The symptoms associated with the foreign body effect of the cysticercus in the tissues frequently do not develop until the worm is dead and calcification has occurred.

The sites where they are most usually reported are (i) in the subcutaneous tissues where they form lumps that are clinically recognized (ii) in the brain where they produce a number of symptoms from mild mental changes such as deterioration of memory to Jacksonian epilepsy and total

mental degeneration and are recognized by x ray examination of the eyes where they may actually be seen in the anterior chamber, (iv) and in other tissues such as the muscles, they are recognized accidentally during x ray examinations or post mortem.

There have been reported several instances of the similitude in man of the plerocercoid (sparganum) larval form of *Bolæda*, probably not of the species *Diphyllobothrium latum* but species such as those that live in lower vertebrates, these may be mild or severe symptoms according to the site in which the parasite is found. The condition is sometimes known as 'sparganosis'.

#### DIAGNOSIS

In *T. solium* infections this will usually depend on the finding of the proglottids in the stools or on their presence being reported by the patient and in *D. latum* infection by the finding of the eggs in the stools.

In *T. solium* and *T. saginata* infections eggs will occasionally be found in the stools but this finding must not be expected. The eggs are practically identical and for differentiation one must rely on examination of the mature or gravid proglottids. This can be done by flattening them out on a slide placing a coverslip over them examining the uterus and counting its primary lateral branches in *T. solium* there are 7 to 13 primary branches and in *T. saginata* 15 to 20 (figure 59).

After unsuccessful treatment that leaves the olex *in situ*, proglottids usually reappear in the stool within three months.

On the other hand the eggs of *D. latum* may be found in the stools but a number of examinations will

have to be carried out before a negative diagnosis can be made as the eggs are extruded by the worm intermittently. In this infection proglottids are not usually found in the stools in an untreated case the most common being most

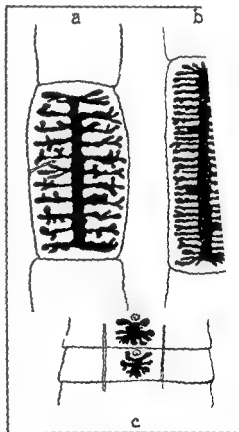


Figure 159 Tapeworm proglottids

- a *Tænia solium*
- b *T. saginata*
- c *Diphyllobothrium latum*

The presence of *cysticerci* may be diagnosed by the palpation and/or removal of the tumours in the subcutaneous tissue or muscles, by the symptoms they produce, when they occur in vital tissues or by x-ray examination. The x-ray examination requires special experience, the exposure should be that given for bone visualization with a slight under exposure. The opacity may be produced by a calcified scolex one millimetre in diameter or by a fully developed *cysticercus* as large as two centimetres in length. It will seldom be worth taking a skiagram within 6 years of the probable time of infection.

It has been said that whenever epileptic fits occur in an adult without a history or injury or a family history of epilepsy, *cysticercosis* should always be suspected.

### PREVENTION

If the beef, pork, and fish are properly cooked the *cysticerci* will be destroyed (65.5° C is lethal) and direct personal prophylaxis achieved.

As a measure of general prophylaxis, in most countries meat is inspected. In the United States, two thirds of the beef that is consumed by the public is inspected. In 1930, 0.37 per cent of carcasses were found infected and were condemned, the figure has improved in recent years. Pork is similarly inspected and 'measly pork' discarded.

It is possible to go one stage further back in the matter of prophylaxis and to prevent cattle from grazing on pasture contaminated with human faeces, or pigs from eating human faeces. Regulations to achieve this will be difficult to enforce, but if meat and pork are inspected frequently and when found infected condemned, and the cause of their meat becoming infected is explained to farmers, the economic aspect will probably appeal to the cattle and pig raisers in the sanitary advanced western countries and they will take the necessary steps. However, in eastern Europe, and in Asia where pigs and cattle are allowed to roam freely, the prevention will be much more difficult.

In the case of *D. latum*, though there are many other definitive hosts man is believed to be the most important and the prevention of the sewage contamination of water where edible fish are caught will be an effective preventive measure.

*Cysticercosis cellulosa* is prevented by the immediate and thorough treatment of all infected individuals, and by observation of rigid personal hygiene, especially by those who know that they are infected. In certain circumstances, isolation of the infected individual would be justifiable.

### TREATMENT

Male fern has been the specific for this infection for many years but some improvement has been effected recently in the preparation, the standardization, and the method of administration of this drug.

An unopened bottle of the oleo resin of *Aspidium filix mas*, or better still gelatin capsules containing 10 or 20 minims each of this drug are obtained. The patient is given two ounces of saturated sodium sulphate on an empty stomach at 7.00, 7.30 and (convenient) one 20 minim capsule (or two 10 minims) at 8.00. A dose of 60 minims. Two hours later, food is withheld until the patient has passed a copious stool, which will contain the whole or most of the worm.

The dose for young children is a total of two minims for each year of apparent age. For children of over 100 pounds in weight 25 minims, for children of 150 pounds and under sized adults 45 minims, and for children over 170 pounds the full adult dose of 60 minims is given, this total dose is divided into three equal parts each of which is given in a teaspoonful of sugar.

This dosage will effect a cure in about 80 per cent of cases. If a patient is in hospital, the stools for the next 48 hours should be kept, screened and the debris examined for the scolex. If this is not present, the treatment may be repeated in a week. On the other hand if the patient is at home, it is a mistake to insist on his keeping and searching his stools, as the procedure is very distasteful and is not likely to be done effectively. If he is not cured he will know in due course, in either of the *Tania* infections, if the scolex is not removed proglottids will be passed again in two to three months time and the case of the fish tapeworm there will be a return of eggs to the stools within five or six weeks.

A method of treatment that is undoubtedly very satisfactory from the point of view of the physician is that practised by Dr J S D'Antoni of the Tulane School. After a preliminary saline purge, he gives by duodenal intubation the following mixture—

Oleo-resin of male fern—one drachm  
Saturated solution of sodium sulphate—one ounce  
Mucilage of acacia—one ounce  
Water—two ounces

No further medication is necessary and within an hour the whole worm, usually intact, will be passed. One hundred per cent success can be expected.

Of the other drugs, carbon tetrachloride is the best and after this defer for persons not under hospital treatment of hookworm infection (1943) obtained an 80 per cent cure rate with the former and 54 per cent with the latter. These drugs are less satisfactory from the point of view of the helminthologist because the worms are often disintegrated when passed but they are cheaper, easier to obtain, less unpleasant to take, and probably safer than oleo resin of male fern. It seems very probable that by intubation they would be as efficacious as is male fern by this route.

As	Any anaemia
lo	or a hæmato-
ty	a macrocytic
	liver extract

Given by mouth or parenterally will be indicated

**Cysticercosis cellulosæ**—No specific treatment appears to have any beneficial effect on the pathogenesis. This is to be expected as most of the pathological changes are associated with the death of the worm. Surgical removal is practicable in certain circumstances.

#### PROGNOSIS

In infections by the adult *tæniæ*, the prognosis is excellent, but in *T. solium* infection the danger of auto-infection must be explained to the patient. In established cysticercal infections, however, the prognosis must



always be guarded, as localization in the brain is very common, and may not become evident for many years

Generally, the prognosis in *D latum* infection is also good, and even the severe anaemia that develops in some subjects is easily curable, at least in those who have no background of pernicious anaemia

### THE DWARF TAPEWORMS

**Geographical distribution.**—Both these tapeworms are cosmopolitan in their distribution but *Hymenolepis nana* shows a patchy distribution, with here and there hyper-endemic areas, e.g. in India and Argentina, for which there is no obvious explanation. *H. diminuta*, of which the rat is the true definitive host, has been reported in man, mainly in India, Russia, Japan, Italy, and the southern United States

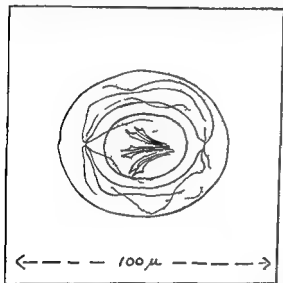


Figure 160 The egg of *Hymenolepis nana*

inner shell with small projections at the poles from each of which arise 4 to 6 filaments and they contain an onchosphere with three pairs of hooklets (figure 160)

An egg is ingested by man, and after passage through the stomach

it hatches in the small intestine where after 3 or 6 days, this larva migrates to the mucous membrane, and develops into an adult (20 to 40 mm in length with a maximum breadth of 1 mm). From the time of ingestion of the egg, the adult worm becomes mature in about two weeks, and when it is mature the terminal proglottid disintegrates and releases about 180 eggs into the intestinal canal. Normally these are passed out with the stools and the cycle is completed, but there is strong evidence that they may hatch in the intestinal canal (whether for this to occur it is necessary for them to be returned to the stomach by reverse peristalsis is not clear), and by a process of endo-auto infection again go through the whole developmental cycle in the same individual. Reinfection by the external route also occurs

***H. diminuta***—The egg is similar to that of *H. nana*, it is sub-spherical, 60 to 80 by 72 to 86 microns, but has a slightly thicker outer covering and no filaments between the two membranes (figure 161)

### ÆTIOLOGY

Both dwarf tapeworms have the same general morphological characters as the large tapeworms

### Life cycles and morphology *H. nana*

—The eggs are sub-spherical, 30 to 45 microns in diameter, they have an outer vitelline membrane covering and an

The egg is ingested by an arthropod intermediate host (a large variety, from grain moths earwigs cockroaches and millepedes to flea larvae, have been incriminated where it develops into an onchosphere and finally a cysticercus in due course the arthropod is ingested by man or other definitive hosts eg rodents in whose intestine it develops into the adult worm (20 to 60 cm in length with a maximum breadth of 4 mm). The mature terminal proglottid disintegrates and releases the eggs which are passed out with the stools.

#### EPIDEMIOLOGY

Man is probably the only important source of *H. nana* infection; it usually is a family, household or institutional infection. Children show the highest incidence. In the United States eggs are found in about one per cent of all stool specimens; in Calcutta a slightly higher infection rate was found and in Argentina a 9 per cent infection rate amongst a group of children has been reported.

*H. diminuta* is relatively rare and is usually associated with low sanitary standards where murine parasites and other arthropods may be accidentally consumed with food. Infection has occurred through the consumption of insects infesting prepared cereal foods (Chandler 1922).

#### PATHOLOGY AND SYMPTOMATOLOGY

*H. nana* invades the mucous membrane during its larval stage secreting toxins and allergins and heavy infections cause a considerable degree of toxæmia which are clinically manifested by convulsions giddiness and even epileptiform attacks. Abdominal discomfort is a common complaint and watery diarrhoea possibly of allergic origin is sometimes associated with this infection.

There is usually a moderate degree of eosinophilia up to 16 per cent.

*H. diminuta* infection is not usually associated with any symptoms.

#### DIAGNOSIS

This is made by the identification of the characteristic eggs in the faecal smear or by the concentration technique (see p 620) or after an anthelmintic treatment—possibly for other worm infections—by the finding of the whole or part of an adult worm in the stools.

#### PREVENTION

Improvement in general sanitation and personal hygiene are indicated. As auto-infection is common special attention must be paid to hand wash-

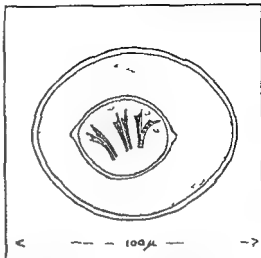


FIGURE 161 The egg of *Hymenolepis diminuta*

ing after stool and before meals. Treatment will also be an important measure, every infected persons in a household or institution must be treated.

### TREATMENT

The treatment of *H. nana* infection is complicated by the fact that both auto-infection and re-infection are common. It is therefore advisable

TABLE VIII  
DIAGNOSIS AND TREATMENT OF INTESTINAL HELMINTHS

Worm	Incubation period weeks	FINDINGS IN FÆCES		Eosinophilia	Drug or drugs of choice and adult dose
		Stage	Constancy		
<i>Ascaris lumbricoides</i> or round worm	8	egg	numerous	++	Oil chenopodium—1 c cm plus tetrachlorethylene— 3 c cm or Hexylresorcinol—1 gramme
<i>Trichurus trichurus</i> or whipworm	12	egg	numerous	+	Leche de Higuerón— 2 ounces or Hexylresorcinol—1 gramme or tetrachlorethylene— 3 c cm
<i>Enterobius vermicularis</i> or threadworm	8	egg	scanty*	+	Gentian violet—1 grain x 3 for 8 days followed by second similar course after 7-day interval
<i>Ancylostoma duodenale</i> or hookworm	5	egg	numerous	++	Tetrachlorethylene in 4 c cm in saturated sodium sulphate—1 oz or Hexylresorcinol—1 gramme
<i>Strongyloides stercoralis</i>	4	larva	irregular	+++	Gentian violet (enseals)— 1 gr x 3 for 17 days
<i>Trichostrongylus</i>	(5)	egg	constant	++	as for hookworm
<i>Tænia solium</i> or pork tapeworm	6-12	proglottid	irregular	++	Filix mas—20 minims x 3 in gelatin-coated capsules by mouth or 60 minims in saturated sodium sul- phate by duodenal tube or carbon tetrachloride— 3 c cm
<i>Tænia saginata</i> or beef tapeworm	10-12	proglottid	irregular	++	
<i>Diphyllobothrium latum</i> or fish tapeworm	5-6	egg	periodic	++	
<i>Hymenolepis nana</i> or dwarf tapeworm	■	egg	periodic	++	Gentian violet—1 grain x 3 for one week or Hexylresorcinol—1 gramme

\*Found in anal swab

to prescribe an anthelmintic that can be taken over a relatively long period or repeated often. Gentian violet meets this requirement best, it is given for one week only in the daily doses recommended for strongyloidiasis (see p 632).

Hexylresorcinol is also a benign drug that can be repeated. It will be advisable to give this in the doses advocated for ascariasis (see p 599), but it should be given twice with a one week interval.

In view of the fact that a multiple infection may arise in an individual from the infection by a single worm by means of auto-infection, even if re infection can be excluded complete eradication of the infection must be achieved. If no eggs are found at weekly examinations over a period of one month cure may be assumed.

For the treatment of *H. diminuta* infection, provided the source of infection has been eliminated, a single efficient treatment will be sufficient. Either of the above drugs could be used, but the oleo-resin of *Aspidium filix mas* is considered to be more specific.

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**Introduction**—Trichinosis or infection with the worm *Trichinella spiralis* (Owen 1835) Failliet 1895 is in no sense a tropical disease. The geographical distribution in fact indicates that a warm climate has some inhibitory effect on the infection, as it is more common in the northern

than the southern United States and is apparently absent from large areas in the tropics where it is hard to account for its absence on dietary considerations alone

prevalent there

The public health importance of the disease has been fully recognized for at least 100 years in the United States. It is prevalent in both of the United States (1943) have shown

### EPIDEMIOLOGY

**Geographical distribution**—Published data probably give a poor idea of the real distribution but it is certainly prevalent in Great Britain (Sheldon 1941) in many European countries and in the United States (from Boston in the north 27.6 per cent to New Orleans in the south 3.5 and 6 per cent). Cases have been reported from Kenya, Uganda and Tanganyika and from Brazil and Chile but evidence that it occurs elsewhere in Africa, in Asia or in Australia is absent. In India, Maplestone and Bhadhuri (1942) reported finding *Trichinella spiralis* in a single cat after failing to find it in 100 dogs, 100 pigs, 100 rats and 73 cats whose diaphragms were examined specifically for this infection by the digestion-extraction technique and after a study of the literature for the preceding 75 years they could find no records of the infection in man or animals in that country.

**Distribution in population groups**—For all practical purposes the flesh of the pig is man's only source of infection and the investigations of Wright and his colleagues (*loc cit*) only showed the infection in one of the two hundred Jews included in their investigation. The infection rate and clinical evidence of the disease is more common in country than in town populations. There are two factors here—the better inspection of the pork in the cities to account for the lower infection rate and the lack of concentration of infected material as would be likely to occur in the country when a heavily infected pig would probably be distributed to a few families only to account for the lower morbidity rate in cities.

**Sex**—In several populations the infection rate has been found higher in women than in men. This has been accounted for by the practice of eating uncooked sausage meat in particular that is apparently common amongst women in these populations.

### ÆTIOLOGY

The causative agent is the *Trichinella spiralis*, a small nematode worm 1 mm in diam and 100 microns long.

**Hosts**—The cycle can be completed in one host species but two individuals are necessary. The common hosts are pigs, dogs, cats and rats and in certain countries bears but any carnivorous animal may be infected.

Rats, which are cannibalistic, are probably the most important reservoir of infection and the pig is the important source of infection to man, although many fatal infections have been acquired from bear meat. Man is only an incidental host and under normal conditions constitutes a *cul-de-sac* for the parasite.

**The life cycle**—Encysted larvæ are ingested, the gastric juice digests the cyst wall sufficiently for the larvæ to escape in the duodenum. They

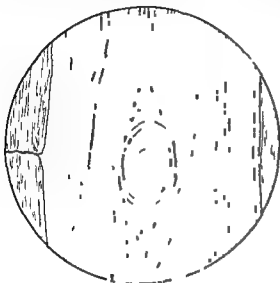


Figure 162: Encysted larva of *Trichinella spiralis* in human muscle

penetrate the mucosa superficially and in from five to seven days develop into adults. The worms mate probably in the crypts; the male dies and is passed out with the faeces, and the female again burrows deeply into the mucosa and parturates producing 1500 larvæ over a period of about six weeks. The larvæ penetrate the lymphatics and venules and eventually reach the systemic blood stream and come to rest in striped muscle. They appear to prefer muscles such as those of the diaphragm, intercostal spaces, tongue, larynx and abdomen that are constantly active (the low glycogen content appears to be the factor, as insulin increases and glucose decreases the number of larvæ that will encyst), but they will also encyst in certain skeletal muscles (e.g. the biceps), and rarely in other organs and tissues. A boat-shaped fibrous capsule is formed around the larva within which it grows to about one millimetre in length and lies curled up (figure 162). The host is then eaten by another carnivore and the cycle is complete (figure 163).

Man may take the place of the host but in this case the cycle will not ordinarily be completed.

**Immunity**—There is evidence that rats acquire an immunity to subsequent infection after the first infection incident. Actual proof that this is so in the case of man is wanting. The morbidity rate is so low, in those who received a heavy dose only first exposure would show any morbidity. However, larvæ of apparently different ages have sometimes been found in one individual.

#### PATHOLOGY

The pathological changes produced in man by this infection can be conveniently divided into three phases. The first phase includes the period of invasion of the infecting larvæ, their development into adults, their mating and the subsequent re-entry of the female into the mucosa. This may cause a considerable reaction in the mucosa with cellular infiltra-

tion oedema some necrosis of the superficial layers of the mucous membrane possibly a little hæmorrhage and considerable outpouring of fluid into the intestinal canal

The second phase commences with the parturition of the female the migration of the larvæ through the tissues their destruction in some tis

the larvæ

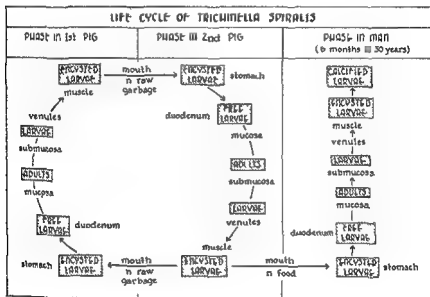


Figure 163

This boat shaped capsule containing the curled up larva lies between the muscle fibres with its long axis parallel to them. Some changes are evident in the surrounding muscle swelling of the muscle fibres proliferation of interstitial tissue or in some cases degeneration of the muscle fibres

In other tissues in which the larvæ are not able to encyst for example in the myocardium and the central nervous system there is evidence that they will nevertheless migrate and cause a very considerable cellular and inflammatory reaction to their toxins, which leads to the destruction of the larvæ, and not infrequently in severe infections to the death of the host

The third phase is a quiescent one cysts will remain viable for a



**Blood picture**—The eosinophil count is constantly high except in debilitated subjects. It may rise to 6000 per c mm (over 60 per cent) in the acute stages, but it will tend to decrease later, however, an eosinophil count of 1000 per c mm or more may be found in an infected subject for several years.

### SYMPTOMATOLOGY

The severity of the clinical picture will vary almost exactly with the weight of the infection, and the vast majority of infections are light and symptomless throughout. On the other hand, there are a few cases in which certain grave symptoms can undoubtedly be traced to cardiac and cerebral involvement in heavy infections, these rarer clinical manifestations will not be described here.

It is convenient to consider the clinical course as being divided into three stages that correspond roughly to the three phases of the pathological picture. Firstly, there is the gastro-intestinal stage which may commence within twenty-four hours of the ingestion of the infected meat and last for several days often overlapping the second stage. This first stage corresponds to the period of activity of the larvæ and adults in the mucosa of the duodenum and probably ends when the female penetrates more deeply and commences to parturite.

The second or the toxæmic stage, characterized by œdema swellings and pyrexia, and later by hæmorrhages, pain in the muscles and other localizing symptoms, commences on the seventh to the tenth day with the parturition of the female and lasts as long as she is discharging larvæ; it covers the period of destruction of the larvæ in unsuitable tissues and their encystment in suitable ones, a period of perhaps six weeks. The subdivision of this stage into two periods that is frequently made in the literature seems to the writer artificial, as the phase in the life of the parasite is a continuous one.

The last is really the convalescent stage, in which the patient is recovering from the effects of the toxæmia, but may have some residual disabilities as a result of the presence of encysted and possibly calcified larvæ.

**The gastro-intestinal stage**—It is apparently only in very severe infections that this stage is prominent. In such cases there is severe watery diarrhœa often with vomiting so that the condition may simulate cholera.

days earlier, but in the majority constipation will be reported.

**The toxæmic stage**—The most constant and prominent symptom is swelling of the eyelids. The patient may wake up in the morning with the eyes completely closed and even with the œdematous conjunctivæ everted and bulging. The rest of the face may also be swollen and there may be swellings in other parts of the body. The conjunctivæ are usually injected.

The temperature is almost constantly raised, usually up to 101° or 102° F, and there is often a remittent type of temperature lasting for one, two or three weeks, or even longer.

There is sometimes urticaria, and other rashes have been described.

As well as severe frontal headache, which is another very constant symptom, lethargy and apathy or anxiety and irritability have been observed in a considerable percentage of cases. Areflexia is frequently observed.

Cough ■ common and hæmoptysis occurs rarely.

About the third day after the swellings have appeared there will often be pain in the various muscle groups, so that breathing becomes laboured, and mastication and deglutition difficult, and in fact all muscular movements, particularly after a period of rest, are painful. Pains may be slight or very severe, and are often described by women as being as intense as labour pains. They may last for one day or for several weeks.

In this stage, if the fever continues for a month or so there will be considerable emaciation and very great weakness with nervous and mental symptoms that suggest the typhoid state.

A somewhat unusual symptom, hæmorrhages under the nails and extreme tenderness of the tips of the fingers, has been noted in about ten per cent of clinical cases.

In fatal cases, death takes place during this second stage.

**The final stage**—In this stage the patient recovers from the weakness and emaciation of the toxæmia and fever. There are often residual pains and muscular pains that may persist for many months and muscular weakness that may last for years. Calcified cysts can seldom be felt but can be seen by careful radiography.

### DIAGNOSIS

This will have to be considered under four headings (a) clinical and epidemiological, (b) parasitological, (c) immunological and (d) post mortem examination.

(a) **Clinical and epidemiological**—A clinical diagnosis is unlikely to be made unless there is an epidemic or the patient gives a clear history of having eaten raw or insufficiently cooked meat that he suspects, but in either of these cases the swelling of the face in the absence of any renal or cardiac cause, the febrile attack in the absence of any demonstrable infection, and the severe cramps in the muscles in the absence of dehydration and hypochloræmia will be highly suggestive. A high eosinophil count without any other apparent cause will add support of this diagnosis.

(b) **Parasitological**—Only by a very unlikely chance will the adults or the larvæ be found in the stools or the latter in the blood or other fluids, e.g. cerebrospinal fluid, but the search for encysted larvæ in muscle biopsy specimens is a useful method of diagnosis, as many ■ 800 larvæ per gramme have been recovered from non-fatal cases. The piece of muscle can be examined pressed between the slides, or after digestion in artificial gastric juice for 24 hours at 37° C (*vide infra*).

(c) **Immunological**—The intra-dermal test has been used widely for

**Technique** The antigen\* is prepared from desiccated larvæ extracted from infected pork

which 0.2 ccm of at least 7 mm rounded by a mm

A control in which the solvent is used without any antigen must be done at the same time

The delayed reaction which may occur after a delay of 24 hours is less specific

The precipitation test is done with dilutions of 1 in 100 upwards of the same antigen. In a micro-tube a small quantity of the antigen solution is floated on top of an equal amount of the patient's serum and the reading is made after one hour in the 37°C incubator. A positive result is a dilution of 1 in 1250 or more suggests recent infection

These tests become positive between the second and third weeks and remain positive for several years

(d) **Post-mortem examination**—The diaphragm is usually the best source of trichinella larvæ. A piece of this is cut into a thin slice which is pressed between two strong slides and then examined under the low power lens of the microscope for encysted larvæ

A more satisfactory method is by digesting the muscles as follows

**Technique** Digest about 50 grammes of muscle in 0.7 per cent hydrochloric acid—1.0 per cent of pepsin 20 ccm to a gramme of muscle overnight. The mixture should if possible be stirred periodically. The digested material is placed in a large glass funnel to which a short length of rubber tube with a stop-cock is attached. The encysted larvæ fall to the bottom of the funnel and can be drawn off by opening the stop-cock. A count can also be made by this method

## PREVENTION

P  
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tion is adequate  
of the value of this procedure

\* from eating lightly  
or 24 hours will  
smoking will not  
practised is the  
lead to it

Education and propaganda amongst small pig raisers in country districts to discourage raw garbage feeding and to encourage the proper disposal of pig viscera and of the carcasses of pigs dying of disease is important. Rats also being common hosts should be destroyed or at least kept away from the animal food store

## TREATMENT

No specific for this infection is known and from the nature of the infection and the difficulty of early diagnosis it seems doubtful whether a specific would be of very great value were one discovered unless it were capable of killing the encysted larvæ in the muscles. Treatment must therefore be symptomatic and palliative

The administration of calcium, in the form of calcium gluconate for example has been suggested in order to hurry the encapsulation of the larvæ

\* Prepared antigen can be obtained from Fh Lilly and Co and probably other drug manufacturers

## PROGNOSIS

It must be obvious that the prognosis in the vast majority of cases is excellent as they do not show any symptoms at all. On the other hand in the very heavy infections in which gastro intestinal symptoms appear the prognosis should be guarded as many deaths have been reported. In such cases the absence of a high eosinophilia is a bad prognostic sign.

It has been estimated that 5 000 larvæ per kilogramme of body weight will usually prove fatal. However 800 larvæ per gramme of muscle have been recovered by biopsy in a non fatal case. The two statements are not necessarily contradictory.

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**Introduction**—Filariasis\* is the term applied to the infections and to the diseases caused by the infections in man and animals by certain nematodes of the super-family Filarioidea that were at one time generally placed in the now superseded genus *Filaria*, namely

*Buchereria bancrofti* (Cobbold 1877) Seurat, 1921  
*Buchereria malayi* (Brug, 1927) Rao and Maplestone 1940  
*Loa loa* (Cobbold, 1864) Castellani and Chalmers 1913  
*Mansonella ozzardi* (Manson, 1897) Faust 1929

For the other two important infections by nematodes of the super-family Filarioidea, namely,

*Onchocerca volvulus* (Leuckart, 1893) Raillet and Henry, 1910  
*Acanthocheilonema perstans* (Manson, 1891) Raillet Henry and Langeron, 1912

the words 'onchocerciasis' and 'acanthocheilonemiasis' are commonly used although both worms are often referred to as filarial worms

The morbid changes that occur in filarial infections are brought about by the mature larvae and the adult worms passing through or lodging in the tissues, especially in the lymphatics and causing local reactions

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\* This section has been written with the aid of some notes by Dr E. E. Rao especially on the morphology of the parasites, on the history and distribution of *B. bancrofti* and on *B. malayi* infection. Most of the photographs were of his department of the Calcutta School of

*Malaysia* is confined to the Americas where it has a limited dis-

Africa and in the coastal areas of tropical and sub-tropical South America. The

No further reference will be made to either of these two infections

## FILARIASIS DUE TO WUCHERERIA BANCROFTI

### Malaysia

### EPIDEMIOLOGY

**Geographical distribution**—Of the human filarial parasites *Wuchereria bancrofti* has the most extensive distribution in the tropics and sub-tropics and occurs in regions from about 42° N to about 38° S in the eastern hemisphere and from about 30° N to 30° S in the western hemisphere.

In America the infection is common in Central America in the West Indies in British, Dutch and French Guiana, Venezuela, Brazil, Peru and Colombia. In the United States a considerable focus of infection probably originally introduced from Africa was discovered in South Carolina some years ago but no fresh cases have been reported in recent years; it probably does not occur elsewhere.

It is common on the west coast of Africa in Madagascar and the neighbouring islands of Mauritius and Reunion in East Africa and in Egypt and North Africa.

In Europe it is reported to occur in Spain (Barcelona), Hungary and Turkey.

In Asia it is especially prevalent in Arabia, India, Ceylon, Burma, the Malayan peninsula, the Philippines and the islands of East Indies, southern China and southern Japan. In some of these areas over 80 per cent of the population are infected.

In India the infection is extremely prevalent but it is more or less confined to the coastal regions and to areas along the banks of the im-



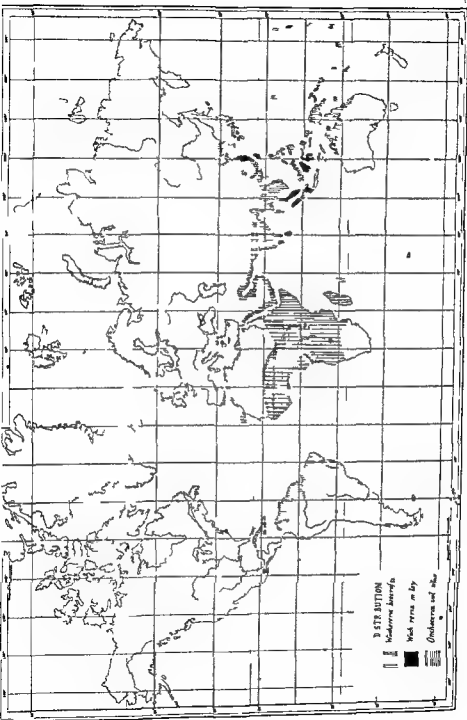


Figure 161 Distribution of Filariasis

portant rivers. West Bengal Orissa Travancore, Cochin and Malabar are the most heavily infected areas (microfilaria rate over 20 per cent).

All these are low flat countries that have a high rainfall they are water logged for many months each year and the temperature and humidity are both high for over half the year, conditions are therefore very favourable for the breeding of mosquitoes and for the transmission of the infection. The moderately infected region (microfilaria rate between 5 and 20 per cent) include the rest of the east coast of India East Bengal the United Provinces, Bihar, and certain areas in the Bombay Presidency such as Surat, Ahmedabad and Thana. Mildly endemic areas include the whole of the Deccan plateau the Central Provinces and Assam. However the intensity of infection is not uniform even within a single endemic area, for instance, in Calcutta the eastern wards of the city show a much heavier infection rate than the central or western wards.

All the areas lying north of a line drawn from Karachi to Delhi are free from the infection these include the Punjab Sind the North West Frontier Province, Kashmir and Rajputana. Elevated regions above 4000 feet are also free from infection.

**Epidemic status**—It is essentially an endemic disease and any rise and fall in the incidence of the disease will as a rule only take place over a number of years. Rises in incidence are usually associated with increases of population or with an increase in the Culex population through ill advised engineering or agricultural undertakings or through a deterioration in the sanitation of the area (*vide infra*) conversely any decline in incidence can usually be traced to improvement in sanitation especially with reference to anti mosquito measures or more rarely to reduction in the human population.

In most places the disease has already found its own level so that it occasionally happens when an infected group of individuals from a highly endemic area migrate or are transferred to an area of low endemicity, there is seldom more than a temporary increase in the infection rate in the local population, if any increase at all is noted. On the other hand when an uninfected population is transferred to an endemic area the immigrants will in the course of years become infected but their arrival will probably not lead to a general rise in the incidence of the disease in the area as occurs in the case of most epidemic diseases.\*

**Seasonal distribution**—In highly endemic areas infection takes place at any time of the year but in the areas of moderate and low endemicity it will only take place at a time when the temperature humidity and other conditions are favourable (*vide infra*). However the time taken for the development of symptoms is so variable and usually so long that the onset of symptoms bears little time relation to infection. In Calcutta the highest onset period was during the monsoon July to September there were 40 per cent more fresh cases than in the cooler-weather months October to February. But this probably indicates nothing more than a lower resistance on the part of the patient at this time of the year.

**Race, sex, age, and occupation**—No definite relations appears to exist between the incidence of infection and the age or sex of the popula-

\*This is the usual experience but when a non infected group lives in close association with a hyper-infected population the intensity of the infection to which they are subjected may lead to a much earlier development of the disease amongst the newcomers.

tion 1

1941)

on the

in hyperendemic areas,\* elephantiasis may commence even at as early an age as 5 years, and, in one case, microfilariae were detected in the blood of a baby of 14 months. In moderately endemic areas, the lesions commence generally between the ages of 14 and 16, and in areas of low endemicity between 20 and 25 years. In general the incidence of infection in women is less than in men. This may be partly due to their conditions of living and their mode of dress.

No special correlation between the incidence of infection and the race or occupation of the individual has been noted. In Calcutta a town of moderate endemicity, it is very rare for the disease to be found amongst European sojourners but it is not uncommon amongst those who have lived there all their lives, and it is as common amongst the poorer Anglo-Indians as amongst the Indians.

### ÆTIOLOGY

**Historical**—The discovery of microfilariae in the hydrocele fluid of a filarial patient was first made by Demarequay in 1863 in Paris. In 1866 Wucherer independently discovered a microfilaria in the chylous urine of a filarial patient in

inside the mosquito in seven days. In 1900 Low demonstrated that the infective larvae escaped from the proboscis of the mosquito on to the skin at the time of a bite. These researches deal with the transmission of the parasite by the mosquito. (Bahr 1912) has shown that the mosquito is the transmitter of the parasite and that the areas of the body which are bitten show that the parasite is the nocturnal intermediary host.

James showed that the filarial parasite in Trivandrum developed in *Anopheles subpictus*. Subsequent investigations, especially those of Cruickshank and Wright (1912) and of Iyengar (1932) have however shown that *Culex fatigans* plays a far more important role in the transmission of *Wuchereria bancrofti* than *Anopheles subpictus*.

\* Endemic areas can for convenience be classed as

- (a) hyper-endemic areas—microfilaria rate 30 per cent or more
- (b) highly endemic areas—microfilaria rate 20 per cent but less than 30 per cent
- (c) moderately endemic areas—microfilaria rate less than 20 but over 5 per cent and
- (d) areas of low endemicity—microfilaria rate 5 per cent or less but an occasional positive finding

**Causal organism**—The adult *Wuchereria bancrofti* are white hair like translucent worms having a smooth cuticle. The male and the female worms live coiled together in the dilated lymphatics the male being considerably smaller than the female. The head is rounded and is separated from the body by a neck like constriction. It is provided with two rows of small sessile papillae. The mouth is without lips and unarmed. The oesophagus has no bulb like swelling at its posterior extremity. The anus is situated close to the posterior extremity of the worm.

Males measure from 25 to 40 mm in length and about 0.1 mm in breadth. The tail is specially curved ventrally. The cloaca is about 0.1 mm from the posterior extremity. The testis is not coiled and terminates as a snowdrop like process which is chitinous in crescent. The long one is cylindrical ending in a glass like swelling throughout gutter like and tremity. There are nine pairs of pre anal and four post anal in position. The caudal alae are sometimes indistinct (Maplestone and Rao 1939).

Females measure from 50 to 100 mm in length and from 0.2 to 0.3 mm in breadth. The oesophagus has no bulb like swelling at its posterior extremity. The anus opens about 0.2 mm from the tip of the tail. The vulva opens on the ventral surface about 0.6 mm to 1.3 mm from the anterior end. The uterus contains eggs and embryos in various stages of development.

**The ova and embryos**—The ova are found in the posterior end of the uterus. Their dimensions vary according to the stage of their development when fully developed they measure about 40 microns in length and 20 microns in breadth. The ovum does not possess a true shell but only a membrane which becomes stretched to form the so called sheath of the microfilaria.

is 359 microns (Iyengar 1939).

The embryo shows well marked cuticular striations. The cephalic space is generally smaller than the breadth of the embryo in this region. The tail tapers gradually to a rounded tip and is free from nuclei.

\* Microfilarial periodicity. The maximum number of microfilariae is found between the hours of 10 P.M. and 2 A.M. and never during the day. This periodicity is a device on the part of the filarial worm (or of Nature) to aid propagation of

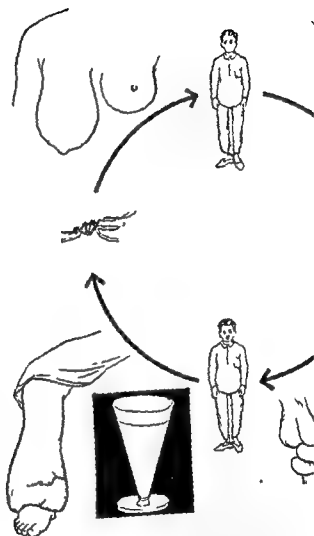


Figure 165 Showing cycle of transmission and infection produced (including chyluria)

Fiji, Samoa, and other Pacific islands where they show no special periodicity. They do not develop further in the blood, but are taken up by the intermediate host the mosquito, where the next stage of development occurs.

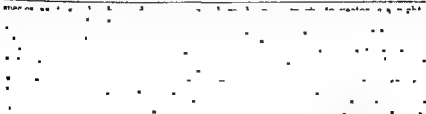
Ordinarily, a drop (20 mm of peripheral blood of an infected individual may contain anything up to 600 embryos. It has been found that, while a moderately high concentration (about 15 embryos per drop of blood) is necessary for the successful transmission of the infection, a much higher concentration of microfilariae, viz, 100 or more embryos per drop, is fatal to the mosquito.

The development of the filarial embryo in the intermediate host, the mosquito, may be briefly described as follows:

As the mosquito feeds on the blood of an infected individual, the embryos (microfilariae) are taken in by the mosquito and enter its stomach. With the progress of digestion in the stomach, the blood plasma becomes thickened. At this stage the embryos escape from their sheaths and enter the thoracic region of their mosquito host. It has been shown by Iyengar (1939) that within ten minutes most of the embryos enter the thorax and lie in between the thoracic muscle fibres, where at first they are comparatively inactive. After two days the first larval stage embryos measure about 124 to 250 microns by 10 to 17 microns. Many changes take place in the structure of the embryos, and the tail becomes reduced to a stump (sausage stage). After the third day, the development of the body cavity, oesophagus and the anus takes place and at the end of seven days the larvae (second stage) measure 225 to 300 microns by 15 to 30 microns. Caudal papillae are now observed.

During the second week, moulting occurs and under optimum conditions the metamorphosis is complete by the tenth or eleventh day. The infective third stage (filariform) larvae which now measure 1500 to 2000 microns by 18 to 23 microns show an alimentary canal and a tri-lobed tail. They leave the thorax, migrate to the proboscis, and eventually reach the interior of the labium. They are generally seen to move in pairs. When the mosquito feeds, the larvae escape at the junction of the labium with the labella (figure 166) and enter through the puncture made by the mosquito or even through the unbroken skin.

The larvae find their way into the peripheral lymphatics. Their subsequent progress and eventual fate will depend to a great extent on the host's reaction, but under conditions of perfect symbiosis the cycle will be completed as follows. The larvae migrate centripetally and eventually reach the large lymphatic trunks where, having developed into male and female adults, they mate. The female parturites and the microfilariae are



If the host changes his habits and sleeps during the day, the microfilariae that he harbours will change their periodicity correspondingly in about three days.

carried *via* the lymphatic trunks into the subclavian veins and the systemic circulation

This is the outline of the cycle as it occurs when symbiosis is perfect and it accounts for none of the pathogenesis associated with the infection when the host's tissues react to the presence of the worm, these reactions and their effect on the cycle will be described below under the heading of Pathology

It is, however possible that in some instances after the adult worms have mated they, or at least the females migrate centrifugally to the lymphatics of the extremities and genitals to parturite This hypothe



Figure 166 Infective larvae emerging from the tip of proboscis of *Culex fatigans*

sis—for which there is analogy but no experimental proof—would help to explain certain observed phenomena though it is believed that these can be explained almost as well on other grounds (*vide infra*)

From the entry of the mature larvae to the appearance of microfilariae in the blood of the host the interval is usually stated to be about one year but there is evidence that it may be much longer

**Correlation between filarial infection and filarial disease**—It is no longer necessary to discuss this from the point of view of establishing the etiology of the disease and the various clinical manifestations one of historical interest of filariasis are concerned

Many of the early workers *e.g.* Low (1908) and O'Connor (1923), noted the correlation between the incidence of filarial disease and the blood

microfilaria rate in the community and recently Iyengar (1938) found a positive correlation coefficient of +0.7644 between the microfilarial rate and filarial disease in 216 localities in Travancore (India). In chyluria due to filarial infection microfilariae are usually found in the peripheral blood. Ray and Rao (1938) found them in 78 per cent of their cases.

On the other hand most (though not all) observers have found a very definite negative correlation between blood microfilarial findings and elephantiasis in the individual. In India Acton and Rao (1930) found microfilariae in only 5.7 per cent of cases of frank filarial elephantiasis whereas they found them in 14.7 per cent of the symptom free population of the same area. In a population in which there was a 92.8 per cent filarial disease rate Rao (1941) found a microfilaria rate of 8.4 per cent in those

**elephantiasis**

The absence of microfilariae in the early stages of the infection must be attributed to the immaturity of the filariae and/or to their failure to mate. The usual explanation for the lower microfilaria rate among subjects with

... can make more easily the finding of an occasion in pregnancy

all the larger lymph channels from the periphery in order to explain the absence of microfilariae in the peripheral blood it is possible that one must visualize a general reaction of an allergic or an antibody\* nature on the part of the host otherwise one would expect the worms in those areas where the blocking was as yet incomplete to provide some microfilariae. Each of these three alternatives is compatible with the observation of Iyengar (1933) that the longer the duration of the obstruction the lower the microfilaria rate is likely to be.

Conditions favourable to the development of the larvæ in the mosquito.—The stages of the development of the larvæ of *Wuchereria bancrofti* in mosquitoes outlined above require a mean atmospheric temperature of about 80° F and a humidity above 60 per cent. Laboratory controlled experiments by Rao have shown that the development of the larvæ in the mosquito depends directly upon temperature and humidity the optimum conditions for the development have been found to be a combination of 80° F with 90 per cent humidity. Under these conditions the parasite is found to complete its full development in the mosquito within seven days. Observations carried out in India (Calcutta and Cuttack) and in China have shown that the times for development in the mosquito under natural

x that are retained in the tissues behind in the subcutaneous tissues are actvely fixing (*sensu lato*) stimulus, whereas in reach the blood stream where they circu

They are obsolete and are subjected to a gradual process of absorption with other circulating debris.



it is converted into a mass of granulation tissue and no longer contains any lymphoid tissue (figure 167). As the lymph channels are obstructed by this granulation tissue, lymph can no longer percolate through the node, nor can the larvae pass through it, they are held up distally to the obstruction and there complete their development. In some instances, adult worms fail to mate and the sterile female, after living in the lymphatics for some time, and causing periodic reactions, eventually dies and is absorbed or calcified. In others, the adult worms mate and the female parturites, in this sub-optimal environment. With the discharge of the embryos, the uterine fluid—which is expelled at the same time—acting as a toxin, causes



Figure 167. Section of lymphatic gland showing sections of filariae in two lymph spaces.

**lymphangitis and/or lymphadenitis** (In sections of tissue containing worms, a large number of desquamated endothelial cells derived from the endothelial lining of the vessel walls can sometimes be seen at the site of the vulval orifice of the worm, which is close to the head end). In this way an obstruction is gradually formed to the centripetal flow of the lymph and the pressure rises in the obstructed lymph channels.

... both to bring embryos intermittently, probably the most likely explanation for the allergic signs and symptoms, both local and general. When the gravid female ceases to produce embryos, toxins are no longer excreted to the same extent as during fecundation and, for the time being, the inflammation subsides.

The primary factor in the mechanical production of lymph varices is this intermittent rise and fall of the lymph pressure. Clinically, such varices are seen most frequently in lymphatics that are supported by loose

tissue such as those around the superficial lymph nodes on the inner aspect of the arm etc. or when the deeper lymphatics are involved the abdominal plexuses and those of the spermatic cord (*vide infra*)

The local reaction to the presence of a foreign body in a lymphatic vessel or in a lymph node may be such that the mature worm or even the

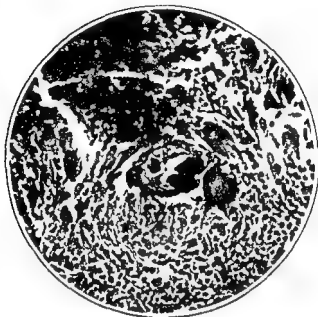


Figure 168. Section of lymphatic gland. Transverse section of filarial worm with giant cells surrounding it

granulation tissue fibroblasts appear and eventually the remains of the worm are encapsulated and may become calcified. This process may be associated clinically with a sharp local inflammatory reaction, and in some cases with a febrile attack. Later there will always be scar formation which will further interfere with lymph flow in this region.

11

all parts of the lymph  
over lymphatic vessels  
the skin lymphatics  
tion and stagnation

results. Lymph ceases to drain from the tissues and the part becomes progressively more swollen. Such tissue is known as blubbery tissue and when one cuts into it the lymph exudes and the tissue collapses.

Drinker and his coworkers (1934-1935) have shown that this lymph has a higher content of plasma protein than ordinary lymph and that this content is further increased by any inflammatory reaction. The high content of plasma protein increases the fibroblastic activity of the tissues

In course of time the fibroblasts in the blubbery skin multiply and form new fibrous tissue which makes the skin dense and hard—the typical **elephantoid skin**. The fibrous induration extends deep down into the lower layers of the skin as far as the sweat glands interfering with the lymphatics in that region and producing oedema followed by fibrosis around the sweat glands which are eventually destroyed so that the skin in elephantiasis is always harsh and dry. In the meantime the surface hypertrophy of the epidermis becomes more and more marked fissures occur in the ill developed horny layer and allow micro organisms to invade the corium. In these very large warty **elephantoid limbs** repeated attacks of inflammation originating at the surface and due to secondary bacterial infection are extremely common and increase the local hypertrophy.

When the obstruction is in the deeper lymphatics the hypogastric and/or the common iliac the lymph is dammed back causing lymph varices of the abdominal plexuses and spermatic cord these may rupture into the peritoneum kidney bladder or tunica vaginalis causing lymph ascites lymphuria lymphocele, or if the obstruction is in the pre aortic nodes through which pass the lymph vessels from the small intestine and some of those from the pelvis of the kidney and which are also connected by small vessels with the lumbar lymph nodes this will lead to a reflux of chyle into these plexuses and if they rupture **chylous ascites chyluria**, and **chylocele** will result.

The entrance of more and more mature filariæ into these dilated tortuous lymphatics keeps up the irritation of the vessel wall so that the endothelial cells hypertrophy and form which projects into the lumen like a papilla. This trauma is likely to rupture the blood vessel and cause bleeding into the lymph vessel hæmatocele, etc.

When the back pressure extends to the lacteals these may dilate and eventually rupture into the intestinal tract this reflux flow of chyle may cause **chylous diarrhoea**, but a much more serious sequel will be infection spread backwards serious septic com

As long as the lymphatic obstruction is only partial or intermittent **microfilaræ** will find their way into the blood stream but if it is complete the larvæ are confined behind the trophic limb and do not appear; that in cases of chyluria and lymphuria almost always found in the blood are frequently not found (*vide supra*).

The importance of **secondary bacterial infection** is a controversial subject. Some workers including Leiper (1924) Acton and Rao (1929) and Grace and Grace (1931) believe that staphylococcal or streptococcal infections play an important part in the processes of a

that most of the the skin can be the body of the part of the host worm itself. All recent work has supported the latter view and has often shown the complete absence of septic organisms in the early inflammatory lesions. The allergic lesions may be some distance from the actual

worm, and the supporting tissues around the genital organs, e.g. the cord

ruptured

**The variations in the lesions produced**—Various explanations have been suggested for the differences in the lesions produced by filarial infections in different individuals, but the following explanation appears to the writer to have most support from his personal experience and from recorded data

If the complication of sepsis is excluded, there are two factors concerned, both of which are variable, namely (a) the tolerance of the subject to filarial metabolites, and (b) the intensity of the infection to which he or she is subjected

The human host will fall into one of the four following categories—

(i) *tolerant individuals subjected to few infected bites* their tissues

(ii) *tolerant individuals subjected to a heavy infection* in course of time mechanical blockage of the lymph nodes may occur causing some static œdema, lymph varix, or both without necessarily any lymphangitis or febrile reaction\*

(iii) *intolerant individuals subjected to few infected bites at long intervals* little damage is caused to the distal lymph nodes since they have time to recover between successive passages of the injected larvæ, all of which nodes, e.g. the which eventually is, or both. The will be found in coccal—infection

occurs that the serious and often fatal acute funiculitis follows

(iv) *intolerant individuals subjected to many infected bites throughout the year* the distal lymph nodes trochlear, are damaged early and do not come to maturity and parturient in periodic attacks of lymphangitis and are completely blocked, with resultant elephantiasis, none or few microfilariae can reach the peripheral blood

There is no reason to believe that tolerance is a fixed quality, and

If now, one of the possible common septic complications is added—such as infection from the skin surface in elephantiasis or from some hollow viscus into which a lymph or chyle varix has ruptured, or possibly

In course of time the fibroblasts in the blubbery skin multiply and form new fibrous tissue which makes the skin dense and hard—the typical elephantoid skin. The fibrous induration extends deep down into the lower layers of the skin as far as the sweat glands interfering with the lymphatics in that region and producing oedema followed by fibrosis around the sweat glands which are eventually destroyed so that the skin in elephantiasis is always harsh and dry. In the meantime the surface hypertrophy of the epidermis becomes more and more marked fissures occur in the ill developed horny these very large originating at th extremely common and increase the local hypertrophy

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The entrance of more and more mature filariæ into these dilated tortuous lymphatics keeps up the irritation of the vessel wall so that the endothelial cells hypertrophy and fr which projects into the lumen like a trauma likely to rupture the blood and cause bleeding into the lymph ves hæmatocele, etc

When the back pressure extends to the lacteals these may dilate and eventually rupture into the intestinal tract this reflux flow of chyle may cause chylous diarrhoea, but a much more serious sequel will be infection of the dilated and damaged lacteals which infection may spread backwards to the larger lymph vessels so that when they rupture serious septic complications are likely to follow

intermittent  
complete

The importance of secondary bacterial infection is a controversial subject. Some workers including Leiper (1924) Acton and Rao (1929) and Grace and Grace (1931) believe that staphylococcal or streptococcal infections play an important part in all the inflammatory processes of a filarial attack where as others question this and believe that most of the milder inflammatory reactions except those originating in the skin can be attributed to the irritation of the filarial secretions and of the body of the worm itself and to an allergic response to these on the part of the host (O Connor 1932) often shown the inflammatory lesions the latter view and has rly inflam the actual

worm and the supporting tissues around the genital organs e.g. the cord and testicle appear to be particularly prone to allergic reaction. The more serious complications however such as acute suppurating funiculitis peritonitis and septicæmia are obviously due to secondary infection which may have been hæmatogenous in origin but is more likely to have resulted from direct infection from some hollow viscus into which the varices have ruptured.

**The variations in the lesions produced**—Various explanations have been suggested for the differences in the lesions produced by filarial infections in different individuals but the following explanation appears to the writer to have most support from his personal experience and from recorded data.

If the complication of sepsis is excluded there are two factors concerned both of which are variable namely (a) the tolerance of the subject to filarial metabolites and (b) the intensity of the infection to which he or she is subjected.

The human host will fall into one of the four following categories—

(i) *tolerant individuals subjected to few infected bites*—their tissues do not react to the filarial metabolites so that the migrations of the pre-adult worm and parturition of the adult cause little or no reaction and no clinical symptoms but microfilaræ will always be found in the blood once the worms reach maturity.

(ii) *tolerant individuals subjected to a heavy infection*—in course of time mechanical blockage of the lymph nodes may occur causing some static œdema lymph varix or both without necessarily any lymphangitis or febrile reactions.

(iii) *intolerant individuals subjected to few infected bites at long intervals*—little damage is caused to the distal lymph nodes since they have time to recover between successive passages of the injected larvæ all of which pass through these nodes to reach the deeper lymph nodes e.g. the which eventually is or both. The will be found in coccal—infection

occurs that the serious and often fatal acute funiculitis follows.

(iv) *intolerant individuals subjected to many infected bites throughout the year*—the distal lymph nodes e.g. the superficial inguinal and epitrochlear are damaged early and obstruct the passage of filariæ which come to maturity and parturite in the lymph nodes of the limbs causing periodic attacks of lymphangitis and fever. Soon the lymphatics become completely blocked with resultant elephantiasis none or few microfilaræ can reach the peripheral blood.

There is no reason to believe that tolerance is a fixed quality and

If now one of the possible common septic complications is added—such as infection from the skin surface in elephantiasis or from some hollow viscus into which a lymph or chyle varix has ruptured or possibly

■ hæmatogenous infection from some septic focus *e.g.* an apical abscess or bowel focus—or if the rarer complications of hæmorrhage occurs it will be seen that a very large variety of clinical manifestations can be accounted for

**Blood picture**—There ■ no characteristic blood picture in filariasis. With the exception of an inconstant eosinophilia any of the changes that occur can be attributed to complications

The sternal puncture count done in a series of 53 cases of filariasis showed about normal percentages for all the blood elements (Napier D Gupta and Rao 1941) the low percentage of eosinophil myelocytes in cases in which there is an increase in blood eosinophils suggests an extramedullary origin for the latter

■ in which there are micro-  
as of lymphatic obstruction  
there is never any increase  
absent from the peripheral

blood

**Microfilariae in the blood**—Reference should be made to the paragraphs on microfilarial periodicity and on the correlation between filarial infection and filarial disease above

We have found fewer microfilariae in the sternal marrow than in the peripheral blood both during the day and during the night

**Urine**—There are no characteristic changes in the urine in an ordinary case of filariasis

In chyluria the urine is typically a milky white but the colour is not constant in a doubtful case the urine should be shaken up with ether or chloroform to see if it clears as it will do if the milkiness is due to fat. If there is any doubt the urine should be examined again one to four hours after a fatty meal. In chyluria is also in lymphuria the urine will coagulate on account of the presence of fibrinogen. If it is set aside it will separate into three strata an upper milky stratum a middle pinkish one in which the clot will be seen and a lower stratum consisting of cells and debris

Microfilariae will be found in about fifty per cent of the cases either in the lowest layer or in the clot or one can demonstrate them by dropping a few threads of cotton wool into the urine allowing these to sink to the bottom and then recovering a thread and examining it under the low power of the microscope

The fat content will vary from a trace to just over one per cent and the albumin from a trace to 0.6 per cent

In lymphuria there is albumin and many lymphocytes but except for the possible presence of clots the gross appearance of the urine is little changed

In hæmatochyluria and hæmatolymphuria there will in addition be red cells and some free hæmoglobin

## SYMPTOMATOLOGY

**Classification**—From the description of the pathological processes given above it will be obvious that the clinical pictures produced may be quite varied. As has been indicated above there may be a short lived skin

lesion—redness and induration with some irritation—at the point of entry of the larvæ, but this is inconstant and is seldom remembered by the patient, it therefore need not be considered in the symptomatology. Otherwise the following classification covers the commonest of the filarial syndromes

- A Signs and symptoms may be absent
- B Lymphangitis and lymphadenitis
  - (i) Uncomplicated
  - (ii) Septic which may subside or lead to
  - (iii) Abscess formation
- C Elephantiasis
  - (i) Uncomplicated
  - (ii) Complicated by sepsis
    - Either may involve
      - a) The limbs
      - b) The scrotum penis or labia
      - c) The mammae
- D Lymph varix superficial or deep
  - (i) Uncomplicated
  - (ii) Rupturing and producing a variety of non septic complications
    - a) Lymphorrhoea of the groin or scrotum
    - b) Filarial synovitis
    - c) Lymphocele (hydrocel)
    - d) Lymphuria
    - e) Lymph ascites
  - (iii) Bleeding as a result of trauma and producing
    - a) Hæmato-permia
    - b) Hæmatocele
    - c) Hæmaturia or hæmatolymphuria
  - (iv) Suppurating before or after rupture
- E Chyle varix
  - (i) Uncomplicated
  - (ii) Rupturing and producing a variety of non septic complications
    - a) Chylocele
    - b) Chyluria
    - c) Chylous ascites
    - d) Chylous diarrhoea
  - (iii) Bleeding may occur as in lymph varix and produce a parallel series of complications
  - (iv) Suppurating before or after rupture
- F General symptoms
  - (i) Fever
  - (ii) Allergic manifestations
    - a) Skin manifestations e.g. urticaria
    - b) Extra focal inflammatory swellings especially of the genitals
    - c) Asthma
- G Psychoneurotic manifestations

A full clinical description of each of the very numerous filarial manifestations classified above would be out of place here but notes are given below on the commoner ones and on those that seem to require some explanation. As far as they are applicable the paragraph identifications used above are followed.

**Incubation period**—It is usually stated that microfilariae first appear

can be obtained from the age at which persons born in an endemic area first show symptoms. In many filarioid countries, it is seldom that evidence of lymphatic obstructions appear within fifteen years of the date of ar-



rival in an endemic area although in such cases there will often be a history of periodic febrile attacks with possibly some lymphangitis for several years. However in highly endemic areas this period is frequently much shorter and recently from the South Pacific cases have been reported in which the incubation period was apparently only three and a half months. Lymphangitis of the arm and of the spermatic cord was associated with fever and the finding of the adult worms but not of microfilariae.

**A Symptomless\* infection**—In most endemic areas the majority of the infections are symptomless and in the areas of low and moderate endemicity they remain so indefinitely. However as fresh infections are superimposed on account either of sheer weight of numbers of adult worms or of developing intolerance on the part of the host some of these subjects will later develop symptoms and naturally the numbers of such persons will vary in direct proportion to the intensity of the infection to which they are subjected (*vide supra*).

**II Lymphangitis and lymphadenitis**—(i) *Uncomplicated*—Attacks may occur at frequent and often regular intervals it is commonly noted by patients that the attacks recur always at some particular phase of the moon or in women at one particular state of the menstrual cycle. The whole limb and the glands in particular are very painful and often a red

of cases. The site of the adult worm may be indicated by a particularly red and tender spot.

The local symptoms are usually accompanied by a febrile attack temperature  $100^{\circ}$  F to  $102^{\circ}$  F with general malaise, headaches and pains all over the body that usually lasts for two or three days. The local symptoms may subside after four or five days.

Not infrequently the general symptoms appear without any definite localizing symptoms and conversely local signs may be unaccompanied by fever.

(ii) If *sepsis*, either hæmatogenous or otherwise, is added the local and general symptoms will be of a more severe nature the whole limb being very swollen and red and the temperature running up to  $104^{\circ}$  F or  $106^{\circ}$  F daily for a week or more. When such an attack subsides the limb seldom returns to its previous diameter.

(iii) A local *abscess* at the site of the dead worm may be left (figure 169).

The bizarre deformities that filarial infection will produce are well known they are capitalized in the East by beggars who parade them for the purpose of obtaining alms and in the West by writers of textbooks who always seek the most extreme examples for decorating their pages



Figure 169 Swellings of filarial abscesses on left arm along a lymphatic vessel

FIG. 169. — Swellings of filarial abscesses on left arm along a lymphatic vessel.

**D Lymph varix**—Varices will occur mainly when the vessels lie superficially or in loose cellular tissue and are therefore relatively unsupported. Lymph varix may thus be found on the surface of a limb or the groin (figure 175) in the spermatic cord in the scrotum or in the deep abdominal lymphatics in the bladder wall or around the kidney.

They may be (i) uncomplicated or (ii) the varix may rupture (a) the surface in the groin or scrotum producing lymphorrhœa (b) into a joint e.g. knee or hip causing filarial synovitis (c) into the tunica causing a lymphocele (hydrocele) (d) into the urinary bladder or the kidney pelvis or calices causing lymphuria or (e) into the peritoneum causing ascites. A characteristic of lymph varices is their sudden disappearance



and reappearance within a few days. Otherwise these conditions are mostly self explanatory, two only appear to need further description.

(c) The varix in the scrotum is under tension and the part that is under tension is kept in the part that is under tension and this keeps it in the part that is under tension.

(d) The onset of lymphuria is often insidious but at other times it may amount to seven or eight ounces a day and the patient's clothes continuously wet.

(e) The onset of lymphuria is often insidious but at other times it may amount to seven or eight ounces a day and the patient's clothes continuously wet.



Figure 174 Elephantiasis of the scrotum

The complications caused by the hemorrhage into the scrotum are mostly on trauma are like those with simple leakage.

The most serious of the septic complications is acute funiculitis and septicemia. It is out of all proportion to the size of the scrotum. It is out of all proportion to the size of the scrotum. It is out of all proportion to the size of the scrotum.

### E Chyle varix

(i) Chyle varix is probably less frequently uncomplicated and symptomless than in the corresponding lymph condition, but it also may be uncomplicated. The condition will usually cause a certain amount of abdominal discomfort, backache, or pain in the loin.

(ii) and (iii) (a) **Chylocele** is also less common than lymphocele but does frequently occur. The swelling will not transmit light and is very likely to be complicated by a certain amount of hemorrhage (**hæmatochylocele**) it might, therefore be mistaken for a strangulated hernia if not carefully examined.



Figure 175 Lymph varix of cord (bilateral) and lymph scrotum

in the bladder that periodically block the urethra. In the case of kidney chyluria the clots may block the ureters temporarily. It is seldom that there is clinical evidence of this but occasionally there will be typical renal colic.

An excretion pyelogram will often show more dilatation of the ureters and during cystoscopy, it is not uncommon to see the clot being slowly extruded from the ureteric orifice. In about three quarters of the cases the dilated lymph vessels can be seen usually just above the ureteric bar but sometimes lower in the trigone.

The chyluric attack usually lasts about a week or ten days and then clears up entirely for some months but sometimes it will last for several

(b) **Chyluria**, on the

other hand is more common than lymphuria. Attention is usually drawn to the condition by the patient's noticing that his or her urine is milky but it may be preceded by back pain and aching in the pelvis and loin. In women the onset of chyluria or hæmatochyluria may follow childbirth and in men any form of physical strain. A very troublesome complication is urinary retention due to the presence of clots

(c) **Chylous ascites** will not be distinguished clinically from ordinary filarial ascites due to the rupture of a lymph varix, but will be apparent when paracentesis is performed. Septic complications are more likely to occur than in the simple ascites and in this case the picture will be one of peritonitis.

(d) **Chylous diarrhoea** resulting from the reflux of chyle into the intestinal canal has been reported but is apparently a rare filarial manifestation

(iv) **Suppurating** It will not be necessary to discuss the septic complications that may be associated with any one of these ruptures of chyle varices but in view of the closer association with the intestinal canal they are likely to be commoner than in the case of lymph varices as has been indicated above

## F General Symptoms

(i) **Fever**—The fever that develops in filariasis is due either (a) to the worm and/or its metabolites entirely independently of secondary infection and for this the accepted expression 'filarial fever' is quite appropriate or (b) to secondary infection of the blocked lymphatic channels of the elephantoid skin or of the varices and for this the expression 'secondary fever' to which the words of filariasis might be added if the context did not already make it clear seems to be unobjectionable\*

(ii) **Allergic manifestations**—There is undoubtedly a form of urticaria that is associated with a filarial attack and often recurs at regular inter-

festations. The writer can give no statistical data in support of this clinical impression

G **Psychoneurotic manifestations**—The psychoneurotic effects were apparent in young white and Anglo Indian girls who living in the poorest parts of certain Indian towns—Calcutta for example—in close association with the native population frequently became infected with filaria but

genital location of the lesion\* (b) occasional associated venereal disease (c) the frequent deformities in the natives with whom they associated (d) the alarming pictures in medical textbooks to whose influence they were too often directly and indirectly subjected and (e) the ill advised publicity given to the whole incident led to the development of psychoneurosis in a very large percentage of those with even the mildest somatic lesions. It has been estimated that 90 per cent of the disability of the personnel invalided on account of the infection were of psychoneurotic origin

\*The fever that occurs when elephantoid skin and tissue become infected has been called 'elephantoid fever'. Not only is the expression 'elephantoid fever' an example of ridiculously misapplied adjective but it is misleading as the fever that develops when secondary infection occurs in other filarial conditions such as lymph or chyle varices has exactly the same etiology and the expression 'elephantoid fever' applied in these cases would be even more ridiculous

# DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

This must be considered under a number of headings —

(a) *Duration of residence in an endemic area.*—The time taken for

(b) *History of a previous attack.*—A history of previous attacks of lymphangitis without any apparent local cause, followed by œdema of the limb that does not always subside, and associated with a mild or severe febrile attack, should arouse great suspicion. Periodic febrile attacks alone in cases in which malaria can be excluded are also suggestive.

(c) *Clinical picture.*—The acute painful descending lymphangitis and lymphadenitis with fever should always be viewed with suspicion in an endemic area, but they may have other causes, the lymph varix, brawny œdema and elephantiasis of the limbs, genitalia, or breasts will be more characteristic, but are only evidence of lymphatic obstruction—the most common cause of which in the endemic areas is, of course, filariasis—and not *per se* of filariasis itself, and certain other lesions that commonly occur in filariasis, such as hydrocele, are as likely to have some other cause even in endemic areas.

When hypertrophy occurs in other regions where there is a good col-

(d) *Laboratory examinations.*—(1) *Blood.*—The examination of the blood for microfilariae has its strict limitations as a means of diagnosing filarial disease, see p 664, correlation between filarial infection and filarial disease.

In countries where the infection is transmitted by *Culex fatigans* or *Anopheles* and the microfilariae show nocturnal periodicity, it is best to examine the blood at night, as in Fiji where it is taken at about 10

*Technique.*—Take about 20 cmm of blood preferably an accurately measured amount from the finger or ear and make a thick smear, dry, then stain and dehemoglobinize. Examine very carefully—do not wash it off—under a low power lens. The number of microfilariae will vary from one in many films to hundreds in one film by multiplying the number per thick smear by 50 the number per ccm will be arrived at.

thread.

The microfilaria of *W. bancrofti* has a sheath. Figure 176 may help in the differentiation of this microfilaria from those of other filarial worms.

No assistance will be obtained from the blood count. Eosinophilia, though frequently present is too inconstant a finding to be of either positive or negative value.

(n) *Immunological tests*—A complement fixation test in which the antigen is prepared from the dog filaria *Dirofilaria immitis* has proved successful but apparently is dependent on the worm being alive.

The simpler intradermal test has been used more widely but there is considerable variation in the technique used. A 1 in 8000 *Dirofilaria* antigen with 0.3 per cent phenol of which 0.01 ccm is given by means of a tuberculin syringe, gives a minimum of false positive reactions even in allergic individuals. A wheel of at least 1 cm in diameter will indicate a positive reaction. A. H. Hamilton (personal communication), basing his opinion on experience in the East Indies considers that positive intradermal tests with *dirofilaria* antigen are of little value since about two out of three normal natives will show positive results. A negative test however he considers to be of the greatest value as excluding filarial infection.

These intradermal tests for which a really satisfactory standard technique has still to be found indicate rather the reactivity of the host than the presence of the worms. Their particular usefulness will not be in a highly endemic area but to diagnose an obscure lymphangitis in a patient who has at one time been in an endemic area but shows no microfilariae in the blood.

A flocculation test with hydrocele fluid has a limited usefulness.

(m) *Urine*—The milky urine in chyluria can be identified with the naked eye. For the method of examination for filaria see p. 672.

(e) *Other procedures*—These include cystoscopy and pyelography to identify the sites of the ruptured lymph varices in chyluria, roentgenography to show the presence of calcified filariae and gland biopsy to identify the adult worm.

#### PREVENTION

This must be considered under two headings—

- A The prevention of the spread of infection and
- B The prevention of attacks in those already infected

A *Prevention of the spread of infection*—The reader should refer back to p. 666 where the essentials for transmission and the factors concerned in endemicity are discussed. These are—

- (i) The source of infection microfilariae in the peripheral blood of man
- (ii) The vector mosquito
- (iii) Susceptible man
- (iv) The links between (i) and (ii) and (ii) and (iii)



This aspect of prevention can be discussed shortly under each of these four headings

(i) Man is the only source of microfilariae, but in highly endemic areas a very large percentage of the community will have them in their blood. Further, there is no drug that has more than a very temporary effect on the microfilariae in the blood. Therefore, any attempt at wholesale 'sterilization' of infected individuals is at present out of the question.

Segregation of infected communities should as far as possible be practised. This may be advisable when labour forces, police, or armies are recruited from endemic areas, and are to be employed in areas where transmission is possible.

Again, the circumstances might be such that it would be advisable to weed out altogether those who had microfilariae in their blood. If this were decided upon, it would be advisable to examine several night blood specimens from each individual.

In endemic areas, the highest infection rate is amongst the poorer classes of people who have made no attempt to protect themselves from mosquito bites, so that the uninfected should build their houses well away from poor-class dwellings and should see that any servants that are allowed to sleep in their houses are free from blood microfilariae.

(ii) Control of the transmitting mosquito will provide the most promising line of attack. While at least a dozen species belonging to four genera, *Culex*, *Aedes*, *Wormorhynchus*, and *Anopheles*, have been found infected in nature and many others have been infected experimentally, *Culex fatigans* is the predominant transmitter in India and in many other tropical countries. It is a night-feeder, a breeder in dirty and stagnant water, and comparatively local in its habits, it is therefore not very difficult to control around dwellings by the usual measures directed against either larvae or

adults, and that some other species is the main transmitter in some regions, but some pages 113

to 117

(iii) There is nothing to be said under this heading as there is little evidence that there is any individual immunity to infection, and there is certainly no evidence that it is possible to induce or increase such immunity.

(iv) In institutions, or even in households, infected persons must be kept in mosquito-proof rooms, or at least under mosquito nets at night, in order to prevent infection of the local mosquitoes.

Conversely, for personal protection in mosquito-ridden endemic areas, screening, mosquito nets, repellents, etc., should always be used, as a precaution against being bitten by infected mosquitoes.

**B The prevention of attacks in those already infected.**—The most

tract, or a bowel lesion, such as c. Elimination of such a focus, e.g. course of carbarsone or diodoquin, of febrile attacks that a patient suffers

This precaution should be taken in all infected persons whether they have suffered previous attacks or not

However as well as by removing septic foci persons who have already had attacks of filarial lymphangitis or some other filarial syndrome can reduce considerably the chances of further attacks by maintaining good general health and if possible moving to a cooler climate. A recommendation to this effect usually can be made with a clear conscience as even if such persons have microfilariae in their blood and there are *Culex fatigans* or other vectors in the locality they will not be a source of danger to the new community amongst whom they go to live provided the temperature and humidity are outside the ranges within which transmission occurs (*vide supra*). It is however quite unnecessary to recommend such a measure as transfer to a cold climate for an infected person who has suffered no clinical attacks except of course as a means of preventing further infection

### TREATMENT

**Introduction**—The treatment of this condition is more unsatisfactory than that of almost any other tropical disease but partly because of this and also because of the variety of the clinical conditions that occur in filarial infection a very great deal has been written on it. It is proposed to treat the subject summarily here. It can best be considered under the following headings—

- A Specific treatment
- B Treatment of secondary infections
- C The relief of lymphatic obstruction
- D Palliative treatment for special conditions

**A Specific treatment**—No true specific has yet been found but there does not seem to be any valid reason why at some future date one should not be expected. Some drugs when given intravenously appear to destroy the microfilariae but this does nothing towards helping the patient for the adult worm which is not in the blood stream is left intact. When the adult worm has once settled in the tissues it is difficult to reach it. The best

for the treatment of the heavily infected

Antimonyl tartrate was used by Rogers in 1917 but it was shown

out success. Systematic clinical experiments with various drugs have been carried out by Rao at the Calcutta School of Tropical Medicine during the last twenty years. Patients at various stages of the infection were treated by drugs whose therapeutic efficiency in other parasitic infection was known. The results may be briefly stated—

Of the organo metallic compounds, soamin (atoxyl) appears to be most satisfactory in controlling the symptoms in the early stages. It can be given subcutaneously, intramuscularly, or intravenously, and is usually non-toxic, although a few exceptionally susceptible persons, who exhibit toxic symptoms even after the first injection have been encountered. There does not appear to be any appreciable reduction in microfilaria count even after a full course of treatment with this drug, but in many cases the patients have remained free from fever and lymphangitis for a long time after treatment with soamin. Certain other arsenic compounds such as tryparsamide, novarsenobillon and sulfarsenol, have given almost as satisfactory results as soamin, tryparsamide, given in 2 to 3 gramme doses, intravenously, appeared to control the symptoms in chyluria in particular.

Practically all available organic compounds containing antimony were investigated. Of these the pentavalent neostibosan\* and the trivalent compound Fouadin gave the most satisfactory results. The latter drug can be administered subcutaneously, intramuscularly or intravenously and is non-toxic. The effect of these drugs on the filarial parasites seems to be temporary, as the microfilariae reappear in the blood after the lapse of some days though it may be several weeks before they reach their previous level. These drugs usually control the inflammation and fever for a considerable time.

drugs used in this disease is antihio

Some workers have claimed good results for several months at least. It is given intramuscularly in doses of 2 c cm to 4 c cm of a 6 per cent solution according to the patient's tolerance, on alternate days up to 10 doses.

Several vegetable drugs which are reported to be efficacious in allied helminthic infections were administered orally and in some cases by injection. Oil of chenopodium appeared to give satisfactory results in some cases when given intramuscularly, it reduced the number of embryos in the circulation and controlled the attacks of lymphangitis but the injections caused painful reactions.

**B Treatment of secondary infections**—This should be considered under the headings—

- (i) Local treatment.
- (ii) General chemotherapeutic treatment.
- (iii) Vaccine treatment.
- (iv) The search for and eradication of septic foci.

(1) *Local treatment* will naturally depend largely on the part affected and the nature of the lesions. Ulcers on an elephantoid leg will in some cases be benefited by elevation of the limb followed by the application of powdered sulphonamide to the ulcerated area and tight strapping of the whole affected part of the limb with elastoplast or some similar material which must be left for several days.

For lymphangitis and lymphadenitis whether there is secondary infection or not hot fomentations and local application of heat by the infra red lamp will relieve the pain and reduce the inflammation.

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\* Recent work by Culbertson and Rose (1945) suggests that neostibosan given in much larger doses than hitherto employed progressively reduces the microfilaria count—to nil in some instances—and that the reduction persists for at least 8 months—the length of duration of observation.

(u) Of the *general chemotherapeutic* agents the new 'sulpha' drugs have proved very useful in the treatment of secondary infections of all kinds and very satisfactory results have been obtained in the treatment of such very serious conditions as epididymo orchitis and funiculitis by the administration of red prontosal, sulphapyridine and sulphathiazole have also proved very effective, but it is probable that new and more effective anti-streptococcal drugs e.g., penicillin will be in general use by the time this chapter is printed

(iii) *Vaccines* have been the mainstay in the treatment of many filarial lesions for some time and it seems doubtful if the good effects claimed and in some cases undoubtedly produced can be attributed to the specific action. The effect has probably in many cases This has ob-  
workers who have used typhoid

A vaccine, consisting of 10 million hæmolytic streptococci of many strains and 50 million staphylococci of several strains of *aureus* and *albus* has been used by Rao at the Calcutta School of Tropical Medicine over a period of 15 years in more than 50,000 cases. The vaccine is given intracutaneously in doses of 0.02 to 0.1 ccm twice weekly up to a total of 15 to 20 injections. The ameliorative effects have been sufficiently encouraging for him to consider that, in the absence of a specific this is the best treatment to give, even when there is no evidence of secondary infection. Other workers have used autogenous vaccines and claim satisfactory results.

(iv) The *septic focus* that gives rise to the hæmatogenous infections should be sought and removed (see p. 670).

**C The relief of lymphatic obstruction**—Attendance to the general health of the patient is important and very often if the patient is sent away to a place with a more bracing climate there will be some reduction in the size of the limb and therefore presumably an improvement in lymphatic drainage.

During an attack of lymphangitis the obstruction is temporarily increased by the inflammation and œdema and the speed with which the permanent fibrotic obstruction develops will depend to a large extent on how long this is allowed to persist so that rapid relief is important. This is helped by rest, elevation of the limb and, if it is not too tender firm bandaging with an elastic bandage. Vaccine and non-specific protein treatment are also useful in this capacity.

For relief in the quiescent stage, surgeons have devised innumerable operations for the re-establishment of lymphatic drainage with little evidence of success. Better results are obtained even at this stage by bandaging the limb tightly. Several forms of permanent bandage have been devised some are made of elastic webbing and others of more rigid material such as muslin or even canvas but fitted with zip fasteners at the top and bottom so that the pressure can be regulated and released when necessary. By this means support is given to the distal lymph vessels and drainage through collateral lymph channels is encouraged, massage and exercise aid this.

**D Palliative measures**—Very often the first demand on the attending physician will be for the treatment of the *acute lymphangitic attack* and this subject has not been specifically covered above. Rest, elevation of the

limb, hot fomentations, infra-red rays or even short-wave diathermy, as such as lead or calamine with aspirin and phenacetin justifiable to give morphine, but it should seldom be necessary to repeat this. A brisk saline purgative, a light diet, rest and the continuance of the local treatment, and perhaps a sleeping draught for the next few nights will be sufficient to help the patient through an uncomplicated attack, but, if there is any evidence or even any suggestion of there being secondary infection, it will be as well to give sulphonamides and possibly the other treatment recommended for secondary infection (*vide supra*).

In certain cases, in order to relieve the pressure—and therefore the pain—during an acute attack, small skin incisions have been made with a very sharp knife and a local anæsthetic under aseptic conditions, through these, lymph drains and relieves the tension, but the procedure is not to be recommended as permanent sinuses may remain and these are not only troublesome to the patient but may later become infected.

The inconvenience and discomfort of massive elephantiasis of a limb will sometimes be relieved by Auchincloss' operation, or some modification of it. In this operation, two parallel skin incisions joined at each end by a V-shaped incision are made in the long diameter of the limb, a wedge shaped piece of skin and blubbery tissue is removed the skin under cut on each side and then drawn together, and the wound closed. If possible

Large scrotal swellings have frequently been removed very successfully, but the operation is not without hazard and should be preceded by a blood transfusion. As these swellings may reach a weight of one, or even two hundred pounds, their removal is a very great relief to the patient. This also applies to elephantiasis of the mamma and vulva, but, if operation is undertaken, nothing short of complete removal should be attempted.

Chyluria should be treated by complete rest, the elimination of all fat from the diet, and saline aperients. If there are clots in the bladder, this may have to be washed out with warm boric lotion of 2 per cent sodium also recom cystoscopy iration has

### PROGNOSIS

Filariasis is not a fatal infection and the expectation of life of the filarial subject is not materially decreased. There are a few of the rarer complications of obstruction of the deep lymphatics such as acute suppurating funiculitis which usually leads to peritonitis, that are very fatal, but they occur in a very small percentage of the persons attacked. Again, in cases of extensive elephantiasis, ulceration and sepsis may cause exhaustion and eventually death.

Many filarial subjects attain a considerable age, and it has even been suggested that the enforced inactivity which the disease may entail actually tends to lengthen the expectation of life.

There is every indication that the serious deformities that are associated with this infection only develop in persons subjected to repeated infection continuously over a number of years, so that even those with heavy initial infections will be very unlikely to develop serious sequelæ if they are removed from the source of infection.

There is no indication that filarial lesions of the genitalia lead to impotence or sterility as, even when there are considerable deformities, vital tissues are not involved.

## FILARIASIS DUE TO WUCHERERIA MALAYI

**Historical**—The embryo of *Wuchereria malayi* was described by Brug (1927) from Java and named *Microfilaria malaya*, and the adults were first seen and described by Rao and Maplesstone (1940) in a biopsy specimen taken from a patient in North Travancore.

**Geographical distribution**—This is a parasite of rural areas with a patchy distribution. *Wuchereria malayi* is the chief filarial parasite in Malaya. It is common in Sumatra, Java, Borneo, Celebes, New Guinea, Indo-China, South China, India, and Ceylon. In India, it is found in a few places in North Travancore, Orissa, the Central Provinces, Santal Parganas, East Bengal, and Cachar (Assam).

## ÆTIOLOGY

there are two pairs of smaller papillæ. There are two spicules which are unequal and dissimilar, and a small boat-shaped gubernaculum.

The female worm measures 55 mm in length with a diameter of 0.16 mm. The mouth is terminal without appendages or lips. The vulval opening is 0.98 mm from the tip of the tail. The general course of the uterus and its branches ending in ovaries is practically the same as in the female of *Wuchereria bancrofti*.

The ovum varies greatly in size, measuring 0.027 mm long and 0.018 mm broad.

The average length of the microfilaria in the fresh state is 263 microns, while in smear preparations it is 186 microns (177-230 microns). The most distinctive character in the microfilaria of this species is the presence of two discrete nuclei at the tip of the tail (see figure 176).

The adult *Wuchereria malayi* lives in the lymphatics of the extremities in man and the sheathed embryos circulate in the blood showing a nocturnal periodicity.

Interstadial stages of the parasite in the blood of man and other hosts are as follows:—  
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 (Ma) .. .. .  
 skin .. .. .  
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 com .. .. .  
 1935 .. .. .  
 grass' (Fraser, 1938) and in Malaya in mangrove swamps.

## SYMPTOMATOLOGY

The pathological lesions produced by this parasite consist mainly of lymphatic obstruction of the extremities. There seems little support for the oft repeated statement that the lesions are usually in the upper extremities in *W. malayi* infection (Rao 1936). Periodical inflammatory attacks

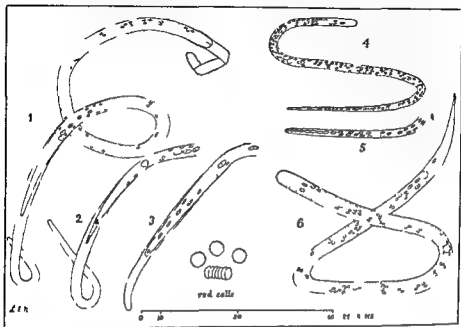


Figure 176. Showing the microfilariae of

Sheathed

- 1 *Wuchereria bancrofti*
- 2 *W. malayi*
- 3 *Loa loa*

Unsheathed

- 4 *Mansonella ozzardi*
- 5 *Acanthocheilonema perstans*
- 6 *Onchocerca volvulus*

of the lymphatic vessels and glands occasionally ending in abscesses are common. No case of genital affection of hydrocele or of chyluria due to this parasite has so far been reported.

## PREVENTION

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## TREATMENT

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## FILARIASIS DUE TO LOA LOA INFECTION

**Definition**—Loiasis or *Loa loa* infection is caused by the filarioid  
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**Geographical distribution**—It has a wide distribution in West and Central Africa particularly along the River Congo and its tributaries. A parasite of the same genus was reported by Mapleson (1938) from India, he gave it the name *Loa inquirenda* provisionally.

**Parasites**—The average length of the male is 30 to 34 mm and the breadth about 0.4 mm. The cuticle is embossed with protuberances. The  
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 d has

The microfilariae exhibit diurnal periodicity and are transmitted by *Chrysops dimidiata* and *Chrysops fuscata*.

The infective third stage larvae appear at the proboscis of these flies in about ten days but their growth to the adult stage in man is believed to take several years and they may live fifteen years.

The baboon also acts as a host to this infection.

## SYMPTOMATOLOGY

Generally the worm infection does not give rise to any signs or symptoms. However in some cases fugitive swellings as large as a hen's egg known as Calabar swellings occur on the course of the worm's migrations. The worms migrate in the arms across the bridge of the nose across the eyeball under the conjunctiva or in any other part of the body. The swellings are hot tender and painful they last for a few days or weeks and then disappear suddenly and they are probably allergic in nature.

Other signs and symptoms of disease produced by this parasite are urticaria hydrocele lymphatic oedema and abscess.

## DIAGNOSIS

For identification. Puncturing or spitting the base around the swellings will often reveal the microfilariae but these are also found in the peripheral blood. The specimen should be taken about midday. Group intradermal and immunological reactions are also positive in this infection.

## PREVENTION

This consists in personal protection from the bites of tabanid flies and measures to control these flies.

## TREATMENT

No drug so far used has any lethal effect on the parasite in the human system. Cold applications of sedative lotions and compresses relieve the



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# DRACONTIASIS, OR GUINEA-WORM DISEASE\*

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\* By the author and Dr ■ Sundara Rao filarians research worker Calcutta School of Tropical Medicine

**Definition.**—*Dracontiasis*, or guinea-worm disease, is caused by the presence of large nematode worms, *Dracunculus medinensis*, in the tissues, it is characterized by a prodromal systemic reaction, local irritation at the site of the worm, septic complications at the point of its emergence, and local fibrotic sequelæ. The disease occurs endemically in certain relatively dry regions in the tropics and subtropics, is very local in its distribution, and is associated with a specific set of conditions regarding water supply.

**Historical.**—Guinea-worm infection is one of the oldest of tropical diseases. The expression 'fiery serpent' in ancient Hebrew literature probably refers to the disease. It seems possible that Moses knew the method of twisting the worm

Dr. J. E. G. wrote stating that in India and Egypt a class of worms called

Our present knowledge about the spread of this infection dates from 1889 when Fedtschenko a Russian biologist in Turkestan, showed that the embryo of

other workers, including Manson who in 1893 repeated the experiments in London and found that the ecdysis of the guinea-worm embryo in the local cyclopids took place in the sixth week. Leiper, working in Africa in 1907, added further confirmation and produced the disease experimentally in monkeys.

In 1913, Liston, Turkhud and Bhaye extended this work further and demonstrated at the Haffkine Institute, Bombay, that a man who drank water containing infected cyclops developed the worm in 348 days.

**Geographical distribution.**—Guinea-worm disease is widely distributed in the tropics. It occurs in Asia, Africa, and South America.

of the Punjab

The disease does not occur at all in the north-east part of India, namely, in Bengal, Assam, and the adjoining provinces, nor in Ceylon, Malaya, or the East Indies (except possibly in some localities in the Dutch East Indies), Australasia, China, or the Pacific Islands. Nor has it been reported from Europe or North America.

#### ÆTIOLOGY

**Morphology of the parasite.**—A fully-grown female worm is 32 cm to 120 cm (12 to 48 inches) long and 1.5 to 1.7 mm (about 1/16th inch) in

diameter. The worm is round, smooth and milky white in colour. The head end is tapering and rounded. The tail, also tapering, is curved like a hook. The mature worm is packed with embryos from head to tail, there are about three million embryos in each worm.

The male worm apparently measures from 12 to 40 mm long and 0.4 mm broad, but few specimens have been seen and these have mostly come from experimentally infected animals.

Embryos are 0.5 to 0.75 mm long ( $1/42$  inch). They have a flattened body and a tapering tail. They lie coiled up on discharge from the worm but they soon stretch out in water and begin to swim vigorously with a tadpole like motion. They can live in clean water for a week and much longer in muddy water. There is no further development of the embryos until they enter the cyclops.

**Life Cycle.**—While in water, the embryos (first-stage larvæ) are swallowed by the cyclops (as many as ten may be seen in one cyclops), and migrate to the body cavity where they undergo further development, at the end of the fifth day the embryos lose their tapering tails, they moult on the 9th day, develop a bilobed tail, and grow much longer. All these changes take about two weeks in the summer months. There is no further growth inside the cyclops.

When infected cyclops are swallowed by man in drinking water, they are killed by the gastric juice in the stomach. The larvæ which were sluggish hitherto become very active and escape from the dead cyclops, they pierce the intestinal wall and reach the loose retroperitoneal tissue where they develop further, and then migrate to other parts of the body of their definitive host. The full development to the mature adult stage takes between eight months and one year.

When the female becomes gravid, it migrates to the surface of the body, usually to those parts that are most likely to come in contact with water—legs and feet. When the worm reaches the site of choice it amongst other things causes a local inflammation. Eventually, when it comes in contact with the air, the uterus prolapses through the y-wall of the worm, appears at the mouth of the opening, bursts, and discharges a milky fluid swarming with larvæ. These pass into the water where they may live free up to about a week, after which they die, unless meanwhile they are swallowed by the cyclops present in the water, when the whole cycle may be repeated.

The discharge of larvæ is determined by temperature, in nature by contact with cold water, but it can be precipitated by the application of a piece of ice, or an ethyl-chloride spray. The migration of the adult worm may also be determined by thermotaxis, as in Rajputana, where *bhisties* (water-carriers) carry water in leather bags on their backs, and worms often appear on the back. In the people who carry water in pots on their shoulders or head, the worm may appear on the neck, or even on the head itself.

Whilst there is no evidence that man ever enjoys complete immunity from invasion by this worm, there is evidence from human experiments in Bombay, in which volunteers were fed large numbers of infected cyclops and only one developed a single worm infection, and from numerous animal experiments, that only a small percentage of the larvæ ingested by man reach maturity.

**Intermediate host (cyclops).—**Cyclopidae are present in many collections of fresh water and are found throughout the year. They breed actively in the summer, they are fairly abundant in the rainy season (July through September), and they decrease slightly in the winter months. They have a pear-shaped symmetrical body with a forked tail, two pairs of antennae, five pairs of swimming legs, and one eye. They measure about a twelfth of an inch and are just visible to the naked eye. There are about six species of cyclopidae in India. They are

*Mesocyclops leuckarti*, *Mesocyclops varicans*,  
*Mesocyclops hyalinus*, *Paracyclops fimbriatus*, and  
*Mesocyclops decipiens*, *Microcyclops karii*

Other species of Cyclopidae in which development may take place include *coronatus*, *magnus*, *prasinus*, *serrulatus*, *quadricornis*, *strenuus*, *vernalis*, *viridis*, and *termifer*. All of these feed readily upon the guinea-worm larvae.

Cyclops thus infected do not live as long as uninfected ones, but they have been found to live up to two months. The average life of cyclops is about three months, but this period is considerably affected by the temperature of the water, and its acidity or alkalinity; they die when the water is warmed to a temperature of 60°C.

#### EPIDEMIOLOGY AND FACTORS IN TRANSMISSION

It will be seen from the above description of the transmission cycle of the water worm, that the transmission of the disease depends upon the following conditions:—  
 (i) the presence of suitable water  
 (ii) the presence of uninfected cyclops  
 (iii) the consumption of the water by the human being, there-

fore —

(a) a very special set of social and sanitary circumstances in which man, firstly, steps barefooted into the water when taking water for drinking or other purposes (theoretically man might contaminate the water by the immersion of other parts, and other animals might act as definitive host) and, secondly, drinks the water from this source without filtration or boiling,

(b) a water source in which cyclops will live and multiply,

(c) the actual presence of cyclops of certain species in sufficient numbers in this water, and

(d) the commencement of the cycle by the introduction of an infected person into the community.

We will consider each of these conditions in association with known facts regarding the epidemiology of the disease.

(a) **Special social and sanitary circumstances**—Dracontiasis is known to be limited in its distribution to towns and villages where such conditions exist.

The water supply of a large number of villages in tropical and sub-tropical countries is from tanks (i.e. reservoirs) or step-wells. At several points around the tank are stone, brick or concrete steps that extend into the tank two or three feet below the water level. It is the local practice to walk down these steps into the water in order to fill the water-pot con-

## DRACONTIASIS OR GUINEA-WORM DISEASE

veniently, even if the tank is reserved for drinking water, which is always the case. In fact, in many instances the villager will first

tank (Figure 177)

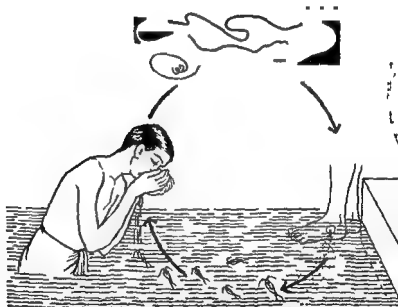


Figure 177 Indicates the transmission cycle in guinea worm disease

The type of water supply in use is often not a matter of free choice for the community, but is determined by soil and climatic conditions. For example, in very dry countries all natural water-supply must of necessity be from deep wells and the disease does not occur.

Finally, educated individuals who have taken the precaution of boiling or filtering their drinking water from these sources have avoided the disease.

(b) **Sustainable water supply.**—Cyclopidae are bottom feeders and do not flourish in deep wells, they require a certain amount of organic matter for their food, they are susceptible to chemical and physical changes in water, they fall an easy prey to fish of many species, and finally, they naturally die out when a well dries up.

The disease is confined to areas of moderate rainfall. Rao has shown that the incidence of the disease is high in areas with rainfall between 10 and 40 inches.

12 inches, there are many heavily infected areas, and the disease never

important part in destroying

Further, the incidence year by year is dependent on the regular recurrence of suitable seasonal conditions, and deviations from these conditions have often been shown to affect the incidence. Instances have been recorded where the disease has disappeared for several years after a flooding, which has washed out the cyclops from the wells, reduced the organic matter, and changed the chemical and physical composition of the water, and similarly after a drought, which has caused the wells to dry up.

On the other hand, in villages in which the normal annual rainfall is on the high side, 30 to 40 inches, a drought that merely reduces but does not dry up the wells will be followed by an increase in the incidence of the disease.

The season when most infections occur is at the end of the hot weather just before the monsoon rains arrive, at this time, the cyclops are present in the largest numbers as the water is shallow and the organic matter is at its highest concentration. Further, the concentration of cyclops makes the water particularly infective at this time of year.

The incubation period is usually about one year, and Rao's collected data show that the curve of the date of onset of symptoms starts to rise in March, reaches its peak in July, and falls again until October, after which it remains at a low level.

(c) *The presence of cyclops*—Conditions may be suitable for cyclops in the temporary or long-standing immune communities has been shown to be washed out by flooding or dried out by drought, it is often several years before the well becomes restocked with cyclops. Experiments with animals and even human experiments (Liston, Turkud, & Bhave, 1913) suggest that a heavy dose of infected cyclops have to be swallowed to ensure establishment of infection.

(d) *Introduction of infection*—Several instances have been reported in which villages in the endemic area have remained free from infection when a well in the village arrived and infected when a well is used by one village or the community may remain free from the disease for some time, until a member becomes infected by drinking from another well.

#### PATHOLOGY AND SYMPTOMOLOGY

FIG. 3. C. A. L. & H. NASSING

where it lies with its head head ... extended along the full length

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... ..

all over the body that is intensely irritating. There is usually a slight

local signs become more prominent. Subsequent attacks, whether in the same season or the following year, tend to be milder, this seems to be against the theory that they are allergic in nature, and suggests rather that the reaction is due to some toxic substance from the worm to which in time the patient develops some tolerance.

The local reaction follows immediately, or is coincident with the general reaction.

The site of the local reaction is usually the ankle or the foot, but varies according to the circumstances. In India, in about 90 per cent of cases the worms point here as these are the parts of the body which commonly come in contact with water, this is probably true of most endemic areas. The worm may appear, however, in other parts of the body also, *e.g.* on the arms, head, neck, chest, back, abdomen, loins, groins, and scrotum, and very rarely on the tongue and eye-lids.

Generally, a patient shows only one worm at a time, and when this has discharged its larvæ or has been removed, the patient enjoys a little respite, until the next year when a fresh worm may appear. Cases of multiple infection are, however, not uncommon. A patient may show two or more worms in the same part or in different parts of the body, either

In one indi-  
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and as many

There is local red induration and vesiculation, and eventually a blister is formed which if the contents are examined will be shown to consist

in the subcutaneous tissues the worm protrudes a portion of its uterus that has prolapsed through its mouth or through a rupture in the body wall near the head, this loop of uterus bursts and the larvæ swim out.

This hole is kept patent by the worm, which at intervals protrudes its uterus and discharges larvæ, it is an easy point of entry for septic organisms, as the uterus is protruded into a septic environment and drawn in again so that secondary infection is certain to occur, but provided the



worm remains alive the local reaction at the mouth of the tunnel in which it lives is not usually very severe. It may amount to an area of redness and induration about an inch and a half in diameter, tenderness, some lymphangitis, and often a little tenderness of the lymphatic glands in the groin. There are seldom any constitutional symptoms.

The worm may, however, die before it reaches the surface, if this occurs, or if the worm is broken while being extracted, there will be a sharp local reaction along the whole length of the site of the dead worm. This may only amount to cellulitis which eventually subsides, or there may be sub-acute abscess formation at different points along the site of the worm, or the site may become secondarily infected and suppurate, with the severe local and general reaction. This suppuration may involve important structures, tendon sheaths, joints, or even blood vessels, and cause serious complications, and even death from pyæmia or septicæmia.

Finally, when the inflammation subsides, there may be fibrotic changes along the whole site of the worm, which may cause scar formation, pain and contractures, or the remains of the worm may become calcified and cause painful lumps, chronic arthritis, tenosynovitis, or neuritis.

The pathological processes can thus be summarized —

- (i) A period of invasion lasting up to a year that is not associated with any pathological changes.
- (ii) A general reaction associated with the discharge of some toxic substance by the mature gravid female worm.
- (iii) A local reaction ending in blister formation in the subcutaneous tissues at the point of discharge of these toxic substances.
- (iv) An area of inflammation and induration due to secondary infection at the point of emergence of the worm.
- (v) Cellulitis, subacute abscess formation, or suppuration along the course of the worm if it dies or is killed.
- (vi) Fibrosis or calcification with various possible complications: chronic arthritis, synovitis, or neuritis.

#### IMMUNITY

There is no evidence that there is any natural, race, class, sex or age, immunity, on the other hand, not all those that swallow infected cyclops suffer from the disease.

In the human experiment referred to above, only one out of five subjects became infected, and very frequently many of the members of a household whose well is heavily infected will escape infection. But Powell (1904) reports an incident in which 21 members of a party drank water from an infected well, during a visit of two days only, seven of them became infected and showed symptoms from 11½ to 13 months later.

As acquired, as many instances cited year after year, in some subjected to infection for a short time each year while visiting their native villages. Again, in a village in Saugor district in India 155 out of a population of 1095 were infected, of these, 121 had single and 34 multiple infections. The large percentage of multiple infections in this village certainly does not suggest the development of any special immunity after the first infection.\*

\* A Poisson series would give only about 15 second infections.

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The fact that the general reaction shows a tendency to decrease with successive attacks has been referred to above, this suggests development of tolerance to the 'toxin' from the worm

### DIAGNOSIS

This will seldom present any difficulty when once the worm has 'presented' and when one suspects the condition, it is often possible to feel the coiled worm under the skin at an earlier date

The diagnosis can be confirmed by the **intradermal test** suggested by G W St C Ramsay (1936), the technique of which is as follows —

**Procedure**—0.1 c.cm of this is injected intradermally

**Result**—A wheel 2 to 3 c.cm in diameter with pseudopodia is considered a positive reaction

The exact position of the worm may be ascertained by injecting it with lipiodol and the x raying the limb. The position of calcified worms can also be demonstrated by skiagraphy

There is usually a marked eosinophilia, up to 15 per cent, but this finding is not specific as it occurs in many other helminthic infections

### PREVENTION

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Definitive hosts other than man seldom play any important part in the human infection cycle. The endless chain man—cyclops—man, can be broken at either link, or the cyclops can be eliminated

For the disease to be transmitted, two elementary principles of sanitation have to be violated, and if either is adhered to, that is, if direct human contact with the drinking water supply is obviated or if the water used for drinking is subjected to even the most rudimentary form of filtration or sterilization, the disease will not occur. Therefore the most important steps in prevention are education and propaganda, but, in the endemic areas in India at least, the habits of the people with regard to washing and drinking are deeply ingrained and amount to a quasi-religious ritual, against which it is difficult to make headway

The next measure is improvement of the water-supply, that is, the replacement of the unsatisfactory water-supply by a satisfactory one. Where possible a pipe supply from a protected source should be installed, but the conversion of step-wells into properly protected draw-wells, or better still into pump-wells, will be efficacious

There will be many instances when from the nature of the terrain or for economic reasons it is not possible to do the other measures.

Measures for the elimination of cyclops may be (i) physical, (ii) chemical, or (iii) biological

(i) **Physical**—The sudden raising of the temperature of water a few degrees will kill cyclops, therefore the bubbling of steam through a well has been suggested and used as a means of control. Unfortunately, the heat that—in practice—it is possible to apply by this means does not kill the eggs of the cyclops, so that the imagines appear in the well again within a few weeks. It is therefore not a practicable measure.

(ii) **Chemical**—Most chemicals have the same limitation, that is they do not destroy the eggs, except in very high unpracticable concentrations. Lime is perhaps the most practicable substance to use as it is often available locally. One drachm of lime in one gallon of water (or about one gramme to a litre) will destroy cyclops. The gallons of water in a well can be calculated from the formula  $4.9 \times u^2 \times d$  where  $u$  and  $d$  are the diameter and depth, respectively, of the well in feet (or see p. 389).

(iii) **Biological**—Fish will eat both the larvae and the guinea worm embryos, and Moorthy and Sweet (1936) used this method successfully for controlling guinea-worm, the species they recommended were *Barbus puckerli*, *ticto*, *sophore*, and *chola*, and *Rasbora daniconius*.

To summarize, control is effected by

- (i) education and propaganda
- (ii) provision of a piped water supply or at least closure of step-wells or as a temporising measure by
- (iii) destruction of cyclops by physical chemical or biological means

### TREATMENT

The aim of treatment should be the destruction of the worm, preferably before it begins to give rise to symptoms, but no drug has yet been shown to effect this. In the absence of a specific the treatment must be aimed at ameliorating the clinical manifestations and preventing the more serious complications of the infection.

It will be convenient to refer back to the six pathological processes summarized on p. 700, and to discuss the treatment in each case, except the first, as in the absence of a specific there is no appropriate treatment at this stage.

(i) **The general reaction**—Fairley and Liston claim that this attack can be cut short by the administration of 10 minims of adrenalin subcutaneously.

(ii) **The local reaction**—This cannot be prevented but it can be relieved to some extent by hot and/or cold applications locally.

(iii) **The local inflammation at point of emergence of worm**—This is to some extent relieved by the worm stage.

(v) **Cellulitis along the course of the dead worm.**—If it is left, the worm will eventually die and, if its removal is attempted inexpertly, it will break and the remaining portion will die, in either case a nidus for septic infection will be left. Removal of the whole worm is therefore the first consideration under this heading.

**Removal of the worm.**—The method of removing the worm that has been practised for generations in the villages where the disease occurs is to wind the head of the worm around a small twig or piece of bamboo, and to give the bamboo one turn each day until the whole worm has been removed. The method is frequently successful, but it takes a long time. Manson suggested a modification in which the uterus is first emptied by encouraging oviposition by repeated applications of ice or cold water to the orifice, so that the worm becomes flat and can more easily be removed by the winding process. There is much to be said for this primitive method, if it is carried out carefully and with aseptic precautions.

painlessly under local anæsthesia.

In the event of the worm being broken, or of a portion being left, its absorption can be encouraged by hot fomentations locally and the administration of sulphonamides to prevent or cure sepsis. Should this fail and abscesses form, these will have to be opened in the usual way.

(vi) **Sequelæ.**—Finally, if the worms become calcified, or fibrotic cords are formed, that cause pain or interfere with the patient's movements, they must be removed surgically.

# PROGNOSIS

sometimes develop fixed joints (ankle or knee) as a result of the prolonged immobilization on account of the inflammation and suppuration associated with the disease, and become cripples for life.

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**Introduction**—Infection with worms of this genus are apparently not very uncommon in animals but up to 1929 only eleven human infections had been reported. Maplestone and Bhaduri (1937) in reporting the fourth case from India expressed the opinion that the infection was probably far more common than had been believed hitherto and quoted the findings of Prommas and Daengsvang (1934) and Castens (1935) in Siam (Thailand). There is thus evidence that the infection is more than a medical curiosity and with a greater awareness on the part of the medical profession a wider distribution of the infection may be recognized.

The infection is not a serious one and the commonest symptom is fugitive swellings in different parts of the body rather than creeping eruptions that are so frequently associated with this infection in textbooks.

**Geographical distribution**—This appears to be essentially tropical. Cases have been reported from Siam (Thailand), India, Malaya, China, Japan and Queensland. More than half the reported cases were observed in Siam.

*In Siam more females than males are affected*

**The parasite**—The parasite is a small worm varying from 1 to 2 mm in length. The immature stages may be only about 0.5 mm in thickness. It has eight rows of hooks arranged ringwise. The larvae measuring less than a millimetre and with only four rings of spines have also been recovered from man. The characteristic heads of the adult and larva are shown in figure 178 on the opposite page.

The full cycle has not been worked out satisfactorily but it would appear that the true definitive hosts are large carnivores: the tiger, leopard, dog, cat and weasel have been found infected in nature. The ova are ingested by a crustacean (cyclops) in which they develop into larvae. A second intermediate host appears to be necessary: fish, frogs and snakes.

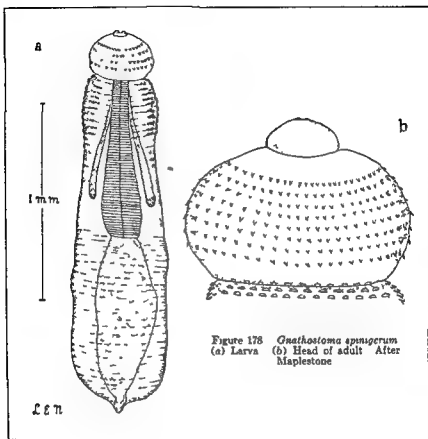


Figure 178 *Gnathostoma spinigerum*  
(a) Larva (b) Head of adult After  
Maplestone

#### PATHOLOGY AND SYMPTOMATOLOGY

the swellings appear within a very short time at points a considerable distance from one another. This continues often for several months, but eventually the worm penetrates to a point just below the epidermis and causes a localized cellular reaction, the site of which becomes secondarily infected and an abscess occurs, when this bursts it releases the worm, alive or dead. Or it may be seen before any abscess has formed, in which case it can be removed without difficulty.

In a large percentage of cases there has been a history that at some time the worm has migrated in the neck and produced a swelling in the

in and sub-  
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other times

pharynx that caused dyspnoea and in one case at least the worm has emerged through the mucosa of the pharynx. In others, hæmoptysis, hæmatemesis, and/or hæmaturia have occurred, without other obvious cause and have not recurred after the worm has emerged or been removed.

Only a very few cases have been encountered in which the worm has burrowed horizontally in the skin and produced a serpiginous itchy raised linear eruption, a condition that could be described as 'creeping eruption'.

#### DIAGNOSIS

This can only be made with certainty by removing and identifying the worm, but a history of migratory swelling should certainly lead one to suspect this infection, especially if the filarial infections can be excluded.

#### TREATMENT AND PREVENTION

There is no known specific, and treatment consists in removing the worm when it shows itself.

Until more is known about the ætiology, no preventive measures can be recommended.

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**Introduction.**—There are two main clinical forms of schistosomiasis namely the vesical and the intestinal. The causal parasites of both forms are trematodes of the genus *Schistosoma* the former is caused by *Schistosoma hæmatobium* (Bilharz 1852) Weinland 1858 and of the latter there are two types which are sufficiently different to warrant separate consideration one caused by *Schistosoma mansoni* Sambon 1907 and the other by *Schistosoma japonicum*, Katsurada, 1904. These parasites are usually known as blood flukes.

**History.**—The Ebers Papyrus referred to hæmaturia that was probably schistosomal in origin and confirmatory evidence of the early existence of this infection in Egypt is provided by Egyptian mummies several thousand years old (20th dynasty).

Bilharz discovered the flukes in the mesenteric veins at an autopsy in Cairo and later he found the eggs in the urine in cases of hæmaturia. Cobbold was the first to describe the worm and he gave it the generic name *Bilharzia* but Weinland's name *Schistosoma* has priority and has come to be accepted although the word bilharziasis is still used by some writers for the diseases caused by these flukes.

Manson and others suspected that there were two species of schistosome on

will two different ... was via the skin

Of the intestinal infections *Schistosoma* ...  
 ... along the south ...  
 ... then inland as far north ...  
 ... especially Leyte and the ...  
 Celebes and in Japan itself were the ...  
*S. mansoni* encountered in north Brazil the Guineas Venezuela and Puerto ...  
 ... along the Congo ...  
 ... eastern part of the ...  
 ... Madagascar

The vesical infection—*S. haematobium*—is distributed widely through Africa, the endemic area extends along the whole of the north coast, up the Nile valley to Abyssinia and down the east coast, taking in the west coast of Madagascar, to Cape Colony throughout which it is endemic, it



Figure 179 Distribution of Schistosomiasis (Simmons *et al.* 1944)

occurs in the tropical countries on the west coast including the Gold Coast, Lake Chad, the Cameroons, and Nigeria, and also at the southern tip of Western Europe, in Spain, and Portugal, and in Palestine, Arabia, and Iraq

## ETIOLOGY

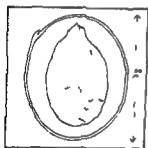
Man is the only important definitive host of *S. mansoni* and *S. haematobium*, but *S. japonicum* has many—man, horse, cattle, dog, cat, rats, and mice. The intermediate hosts are molluscs of several species and a number of genera.

The stages of the parasite that occur in man and his excreta are described on the following page.

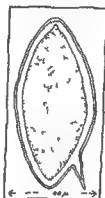
but of about the same breadth. The range of measurements, as given by Craig and Faust (1943), and the distinguishing characteristics of the ova of the three species are shown below

	Range in microns	Special characteristics
<i>S. japonicum</i>	70 to 100 by 50 to 65	Small depression near one pole with in curved hook
<i>S. mansoni</i>	114 to 175 by 45 to 68	Prominent lateral spine near one pole
<i>S. haematobium</i>	112 to 170 by 40 to 70	Distinct spine at one pole

Figure 180 Schistosome eggs



*S. japonicum*



*S. mansoni*



*S. haematobium*

**The cercariae.**—These are materially the same in the three species, though those of *S. japonicum* are smaller. They consist of an oval or fuse-shaped body and a forked tail. The bodies of the cercariae of *S. mansoni* and *S. haematobium* average about 200 microns, their breadth is a little less than half their length, the main stem of the tail is a little longer than the body and about 40 microns across and each prong of the forked tail is about 100 microns long. When they enter their definitive host, they discard their tails and become metacercariae.

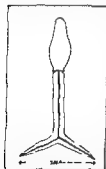


Figure 181 The cercaria of *Schistosoma*

**The adults.**—The males are shorter and stouter than the females, they measure from 7 to 20 millimetres in length and 0.5 to 1.0 mm in breadth and have two unequal muscular suckers, the smaller one at, and the larger on the ventral aspect near the anterior end. Along its whole length the body of the worm posterior to the suckers is folded ventrally to make the gynæcophoral canal, in which the female is held during fertilization and oviposition.

The female is longer and slenderer, it has two suckers in relatively the same position, but they are smaller and not so muscular. The uterus, which contains 20 to 30 eggs at a time, opens near the anterior end.

The range or average of sizes of the adults of the three species is given on the opposite page.

	Size in millimetres	
	Male	Female
<i>S. japonicum</i>	to 20 by 0.50	26 by 0.3
<i>S. mansoni</i>	7 to 10 by 1.0	7 to 14 by 0.25
<i>S. haematobium</i>	10 to 15 by 1.0	20 by 0.25

**Life cycle**—In man the cercariæ are the infective stage. They enter the skin when he bathes or wades in infected water. They adhere

vessel and are carried to the right side of the heart, and thence via the pulmonary artery they reach the lungs. They may also enter through the

### LIFE CYCLE OF *SCHISTOSOMA MANSONI*

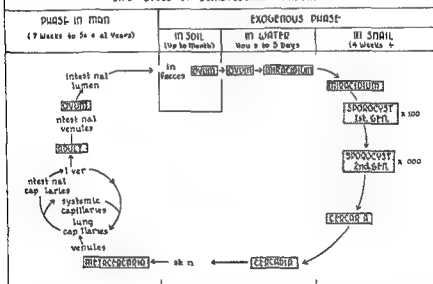


Figure 182

buccal nasal or pharyngeal mucous membranes in persons drinking or washing out their mouths with contaminated water they would not however survive passage through the stomach. In the lungs they negotiate the lung capillaries and cross over to the venous side they are carried once more to the heart and thence into the systemic circulation. Apparently only those larvæ (meta cercariæ) that get into the right traffic lines and find themselves in one of the mesenteric arteries have any future these on reaching the intestines negotiate a second set of capillaries and crossing over to the portal system reach the liver. It is thought possible that some pass through the liver and make another cycle before finally coming to rest in the liver. (The larvæ that fail to reach the mesenteric arteries on the first round probably do not survive long enough to make another complete circle and negotiate three more sets of capillaries but die and are removed with other blood debris). When the larvæ reach the liver they begin to feed and develop they do not however remain here but turn back into the portal vessels and migrate against the blood stream.

Up to this point the route taken by all three species is the same, but subsequently their behaviours differ. The larvæ of *S. japonicum* when they reach the superior mesenteric vein turn into the ileo-colic or the colic branches, here, having reached maturity and mated, the female, who is held in firm embrace by the male, stretches her head end, which is directed towards the capillaries, into the venules of the mucous membrane of the small intestine and upper part of the large intestine, and from her vulval opening, near the head, deposits eggs one by one. She then moves to another site and repeats the process. The miracidia within these eggs secrete a lytic substance which percolates through their shells and causes local tissue necrosis and eventually ulceration, from this ulcerated area the ova find their way into the lumen of the gut, and are passed out in the stool.

On the other hand, *S. mansoni* flukes migrate further, into the inferior mesenteric veins, and oviposit in the venules of the mucosa of the descending colon, sigmoid, and rectum, the subsequent course of their ova is the same as those of *S. japonicum*.

Whereas *S. hæmatobium* flukes go further still, and, via the hæmorrhoidal plexus, finally reach the vesical and pelvic plexuses where they oviposit into the venules of the mucosa of the bladder, the ova break through into the bladder and are passed in the urine. The course taken by the majority in each infection has been indicated, but there is some overlapping and in *S. japonicum* infection there will be many instances in which the adults migrate in the inferior mesenteric vein and deposit their eggs in the mucosa of the descending colon and rectum, but they never reach the vesical plexus. Conversely, *S. hæmatobium* ova will sometimes be found in the rectum, but are rarely deposited in radicles of the superior mesenteric vein.

**First free-living phase**—When the ova, passed in either stools or urine come in contact with water, from each a single ciliated larva (or miracidium) hatches out. These larvæ, which are approximately the size and shape of the ova, are actively motile, but are unable to feed and only live about 16 hours.

**In the snail**—They are attracted to certain species of snails (probably by a specific exudate of the latter) whose soft tissues they enter. The miracidia enter the lymphatic vessels of the snails, there they lose their cilia and develop into sporocysts (first generation). The worms develop for 4 to 8 weeks in the snails, mainly in the liver, passing through two sporocyst stages, finally innumerable (up to a quarter of a million) fork-tailed cercariæ burst out of the snail in swarms, daily, over a considerable period, placed at over 60 days by some observers.

**Second free-living phase**—These cercariæ, which are only discharged 1 to 3 days, swim vigorously, but they cannot live more than 48 hours on average.

ing 24 hours and at most three days, themselves to the legs of a bathing or tive host, discard their tails, and, by into his skin to commence a new cycle.

**The time factor**—This can best be appreciated by dividing the life cycle into different stages. The migrations of all three species up to the time they reach the liver is about five days and the adults of all three species become mature within three weeks from the time of entry of the lar-

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### *S. haematobium* infection

**Variations in the cycle**—While the above is the ideal cycle from the point of view of the worms the ova and more rarely the adults will reach a number of other sites. Very frequently ova become detached from the intestinal venules and are carried back into the liver; this occurs much more constantly in *S. japonicum* infection in view of the proximity of the superior mesenteric vein. In the latter infection in particular, the ova and even the adult worms may negotiate the liver sinusoids or the collateral portal anastomoses and via the systemic circulation again reach the lungs, or they may be carried to and lodge in other organs and tissues e.g. the brain.

**The intermediate hosts**—Craig and Fauet (1943) give the following as actual or potential hosts—

For *S. haematobium* *Bulinus truncatus* (Egypt, Cyrenaica and Tunis), *B. forskalii* (Mauritius, and possibly Kenya colony) *B. tropica* (South

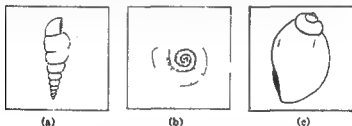


Figure 183 The snail intermediate hosts of Schistosomes

(a) *Oncomelania* of *S. japonicum*

(b) *Planorbis* of *S. mansoni*

(c) *Physopsis* of *S. haematobium*

Actual size of average specimens

Africa), *Physopsis africana* (South Africa and the Belgian Congo) *P. globosa* (Sierra Leone, West African Coast, northern Nigeria, Nyasaland and Rhodesia) *P. nasuta* (Kenya Colony) and *Planorbis dufour* (Portugal and Morocco)

For *S. japonicum*, *Katayama nosophora* (Japan and along the coast of China), *K. formosana* (Formosa), *Oncomelania hupensis* (Yangtse basin), *O. hydrobiopsis* (Leyte Philippine Islands)

### EPIDEMIOLOGY

The disease occurs mainly amongst populations with a low sanitary standard or where human faeces in a relatively fresh state are used for

manure. In some of these populations the infection is very intense, involving as much as 90 percent of the people, as for example in some parts of the Nile valley, and in Egypt as a whole it has been estimated that six million persons, or about half the populations are affected either by *S. haematobium* or *S. mansoni*, whereas in the heavily populated Yangtse valley tens of millions of Chinese are infected.

The persons most frequently affected in the endemic areas are fishermen, rice-field workers, washermen or -women, and bathers of any kind including ceremonial (Mohammedan) bathers.

Amongst foreign sojourners and visitors, the infection is often contracted by sportsmen, whilst wading through streams or flooded rice fields, by sailors\*, whose duty necessitates their wading in contaminated water, and by pleasure seekers and children in particular, who may wade or bathe in polluted waters.

Instances have been reported, e.g. in Egypt and Puerto Rico, where sporadic cases have occurred amongst the general population of towns, and have been traced to cercaria-infected piped water supplies.

Persons of all ages and races are susceptible, but there is frequently a male predominance, and children appear to be very susceptible.

The season of highest infection in the Nile valley is from February

#### Factors determining the incidence of the disease

The essentials are (i) The sources of infection, man is the sole reservoir of infection for *S. haematobium*, and probably the only important one for *S. mansoni*, although monkeys have been found infected in nature, but for *S. japonicum* there are other important sources, for example, cattle, especially water-buffaloes and in Japan field-mice are incriminated, but the relative importance of these non-human sources does not seem to have been estimated.

(ii) The presence of snails of certain species to act as intermediate hosts.

(iii) Promiscuous defaecation and/or urination, a sanitary system by which waterways are polluted, or the use of human excretions for manure.

(iv) The practice of bathing, wading or standing in polluted water, or drinking or washing out the mouth with water taken directly (i.e. without storage for at least 3 days) from a polluted source.

(v) Climatic (especially temperature) conditions that are favourable to the development of the parasite in the snail and to its survival during its free-living stages.

The extent of the incidence of the disease present in any locality will depend on the degree to which these factors are in operation. In many places

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latrines for example, are built over the streams so that urine and faeces fall into them or they are used as the main sewer. And in China human excreta are stored in large earthenware jars and used as manure in the rice fields. If in such areas suitable snails happen to be present, the incidence of the disease is certain to be very high indeed. In other areas, where pollution is a rare incident the disease will be sporadic and unimportant.

Where the specific molluscan hosts have only a limited distribution as in certain places in Japan, the disease is localized.

From time to time new areas have become infected through snails migrating or being carried into areas where although climatic, sanitary and social conditions were already suitable the right species of snails did not previously exist.

The male predominance in some places in China for example is due to the fact that boys bathe in canals whereas the girls are not allowed to do so. Also on the whole the occupation of the men exposes them more to infection.

### PATHOLOGY AND SYMPTOMATOLOGY

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There are very considerable variations in the reactions of the individuals to the infections. In Egypt, for example, a certain degree of tolerance to infection is observed.

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that there are

It is usual in order to facilitate description to divide these pathogenic reactions into stages, this device is a useful one provided it is fully appreciated that not only will one stage run into the next, often imperceptibly, but that in an endemic area where fresh infections are repeatedly occurring the stages will be continually overlapping one another.

The division which seems the most logical is as follows —

I. The period of invasion and development of the parasite, up to the time the flukes reach their habitat of choice and develop into the adult stage. Clinically this is the incubation period during which however, at the time of the first invasion, mild symptoms of a local nature may occur, these prodromal symptoms are not constant and are almost certainly absent in the native of the endemic area who has been previously infected.



II. The period of egg deposition, associated with an immediate in-  
 the part of the host's tissues to  
 the adult flukes, and possibly to  
 clinical picture associated with  
 this includes a generalized febrile reaction a skin eruption, and liver en-  
 largement in all three infections, and usually a little later, as the eggs are  
 extruded into the intestinal lumen, dysentery, in *S japonicum* and *S man-  
 soni* infections, or urinary symptoms, as the eggs are extruded into the blad-  
 der in *S hæmatobium* infection

III. Period of fibrosis and attempts at tissue repair.—In this stage,  
 the most serious and varied complications, with irreparable damage to many  
 organs, occur

The pathology and symptomatology are described separately below,  
 events, without separation into  
 the divisions come Further, in  
 of the three different infections  
 are the courses of the parasites  
 diverge

#### PATHOLOGY

Skin.—At their point of entry, the meta-cercariæ usually produce no  
 gross pathological lesions, but in experimental infections minute petechiæ  
 can sometimes be seen with a hand-lens However, after a short time when  
 they have penetrated into the skin proper, they call forth a local tissue  
 reaction which destroys a certain proportion of the cercariæ, and their  
 bodies, then acting as foreign protein, give rise to local allergic manifesta-  
 tions—urticaria and œdema This reaction is much more noticeable in  
 foreigners than amongst the local native population

It is of interest that this skin reaction is also much more severe and  
 is likely to develop into a dermatitis in the case of the cercariæ of schis-  
 tosome that are not the natural parasites of man and fail to establish  
 themselves in his tissues, e.g. *Cercaria elia*, reported in the United States  
 (Lake Michigan), and *Cercaria ocellata* from Wales and elsewhere in  
 Europe, which cause cercarial dermatitis but no visceral infection In these  
 cases, the meta-cercariæ are probably all destroyed locally and give rise to  
 the maximum reaction

Lungs.—Again, the passage of the lung capillaries is apparently ac-  
 complished without causing much local reaction, by the majority of the  
 larvæ, but others break through into the alveoli where they may cause  
 hæmorrhages and local reactions in the submucosa of the alveolar walls  
 pneu-  
 tensive

General reaction.—When, however the larvæ reach the portal vessels  
 and develop into adults, they cause a generalized reaction that is frequently  
 the first evidence of the disease This reaction seldom appears before the  
 end of the third week and is sometimes delayed for as long as three months,  
 it is caused by metabolites from the adult parasites, some of which are  
 probably associated with the parturition of the females This reaction  
 occurs only during the invasion of the first crop of parasites or, if it is re-  
 peated, it is much milder, so that apparently the individual becomes de-  
 sensitized to the toxic agent, whatever it is The reaction is associated with  
 hyperæmia and hyperplasia of the liver and often of the spleen, and a very  
 marked eosinophilia, 10 000 per mm (circa 60 per cent) or more

**Local reaction to the ova**—Where this reaction takes place will naturally depend on where the eggs are deposited and this will vary with the species of the infecting flukes (*vide supra*)

the venule and often abscess formation. Around these abscesses giant cells and fibroblasts appear. This process occurs in the mucosa and sub

the muscularis into the sub mucosal papillomatous growths

stools

The eggs are also deposited in the muscular coats where they produce the same infiltration abscess formation and fibrosis and sometimes they calcify so that in time the whole wall of the bowel may become a thickened and hard more or less functionless tube. These deep ulcers with their bases in the muscular layers may in time heal leaving scars that later contract and may cause obstruction. In these later stages any dysentery that occurs will usually be associated with intestinal strictures and the diarrhoea which is a common terminal event will be due to mucosal dysfunction and malabsorption.

Finally the serous coat may be involved there will be a fibrinous exudate on the surface which results in adhesions forming between loops of viscera. The mesentery and the retroperitoneal tissues are also involved as well as the lymphatic glands in both these situations. Subsequent fibrosis and contracture will tend to produce further intestinal complications.

A large number of eggs find their way back to the liver probably because it would be difficult to pass them in the stools. In the liver the eggs are surrounded by a capsule and are even surrounded by the metabolites from the adult flukes lead to the production of at first hypertrophic and later cirrhotic changes in the liver. Ascites and other sequelae of portal cirrhosis will develop and later when the cirrhotic changes involve the biliary canaliculi jaundice. Thrombosis of the portal vein is not an uncommon sequel.

These changes in the liver will lead to passive congestion then hypertrophy and finally fibrosis in the spleen so that the organ may become

immense. It may contain a few ova, but these are usually insufficient to account for the extreme enlargement which is mainly secondary to the liver involvement. In some cases the splenic vein is thrombosed.

In both the liver and the spleen, the reticulo endothelial cells contain large quantities of hæmatin from the changed blood excreted by the flukes.

Sometimes eggs are found in the lungs, brain and spinal cord, kidney and other organs and tissues, where they produce similar changes.

In *S. mansoni* infections, a very similar series of changes occur, except that the brunt falls on the lower end of the colon, the descending colon,

bowel lesions appear to be absent and only the hepatic and splenic changes are found.

In *S. hæmatobium* infections, most of the eggs are laid in the radicles of the vesical and pelvic venous plexuses, but occasionally the adults wander into the scrotum, and perineum, in these areas. These eggs

they reach water would be if the eggs are placed in the venules of the mucosa and submucosa and cause parallel changes to those of the bladder, so that

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If of the bladder and in the upper layers of the bladder, surrounded by fibrous

tissue, they are later either replaced by purulent whorls or they become calcified. If there are many eggs, the bladder is eventually converted into a rigid and useless bag. Eggs are also deposited in the lower end of the

and may in time cause an obstruction and hydronephrosis, and also surrounding this, where they may cause

nis, and later, if the eggs become calcified, part of this organ may occur. They are they cause hypertrophy, and, in the pelvis,

d and the lymph flow obstructed, so that ha and/or a proliferating warty condition

when the eggs are deposited in the venules of

around the anus may the skin of the groin, scrotum, and perineum, here they cause a papular

eruption which may become pustular. Viable eggs can be found in a smear made from scrapings from these eruptions.

A few eggs may be deposited in the mucosa of the rectum and be extruded in the faeces as in the case of the other blood flukes, but seldom

elsewhere in the intestinal canal except apparently the vermiform appendix (in one series in Nigeria, 57 per cent of the appendices removed contained ova)

In the later stages secondary infection of the bladder is almost the rule, this infection will often ascend to the kidneys and cause pyelitis and pyelonephrosis

Eggs frequently reach the systemic circulation in the infection with this species on account of the fact that the venous return from the areas where they are most frequently deposited is *via* the inferior vena cava, the eggs are usually held up in the lung but sometimes get through to other organs and tissues *e.g.* the brain and cord. In the lungs, an interstitial pneumonitis is frequently caused

**The blood picture**—In the early stages, as already noted, there is a marked eosinophilia and usually little change in the hæmoglobin percentage or red cells, in the second stage, anaemia tends to develop in all three infections and although there may still be a relative eosinophil increase,

reduction in—eosinophils, but sometimes a polymorphonuclear leucocytosis as a result of secondary bacterial infections, though as a terminal event this also will fail

### SYMPTOMATOLOGY

**Schistosomal dermatitis**—At the time of infection, as the water dries on the skin there may be a tingling sensation which is shortly followed by the development of small urticarial weals at the sites of entry of the cercariae.

This is a result of infection with any of the it is not constant and is apparently (only in 10 per cent of the American above it occurs much more constantly is schistosome that does not establish itself in man. The syndrome is known as 'swimmers itch' in the United States (Cort, 1928) and Canada (McLeod, 1940) where it commonly occurs amongst bathers in the big lakes

**The febrile attack**—This occurs between the end of the third week and the end of the third month. It has been reported as early as the fifth day in *S. japonicum* infection, but the experience of others and experimental work suggest that these reports of the very early occurrence of the febrile attack should be regarded as exceptional.

is not so well defined or constant. The onset may be gradual or sudden. The fever usually rises each evening to about 102° and then falls to normal or the 99° line towards morning (figure 184). There are usually chills, and often an actual rigor followed by profuse perspiration during the night. The fever is accompanied by malaise, anorexia, pains in the back and along



endemic areas, the process will be more or less continuous, with a few quiescent periods, during which the symptoms recur immediately when the patient returns to work or otherwise exerts himself, and after a few years (3 to 5 years is sometimes the interval mentioned but it must be very variable) the condition will pass imperceptibly into the next stage.

In the final stage, there is increasing emaciation, debility, anæmia, and dyspnoea. Children show stunted growth and intellectual retardation. The dysenteric condition may continue, but usually takes on the features of chronic ulcerative colitis, there may be some intestinal obstruction with distension of the upper part of the intestinal tract and alternating constipation and diarrhoea. The liver may enlarge further, but usually becomes hard and very fibrotic and tends to contract. The spleen however shows complementary enlargement and may reach the symphysis pubis or the right iliac crest and it also becomes very hard. There are frequently extensive ascites, distension of the abdominal veins, and hæmatemesis results of portal obstruction. The emaciation is profound on account of absorption failure in the upper intestinal tract and liver dysfunction, the patient usually develops a sub-icteric tint and sometimes frank jaundice. Jacksonian epilepsy, hemiplegia, paraplegia and blindness have followed the deposition of the eggs into the brain, the cord, or the optic nerve.

Death may occur from inanition secondary infections, such as pneumonia which may be encouraged by the reaction caused by the ova in the lung, hæmorrhages, or intestinal obstruction or suddenly as a result of the local reaction to the ova in the heart or brain.

*S. mansoni* infection.—The course of events is very similar to that in *S. japonicum* infection, but on the whole the course is not usually so severe, and more symptoms are referable to the rectum. For example,

is not interfered with to the same extent, the pathogenesis being mainly in the large bowel.

In Egypt, hepatic and splenic enlargement sometimes occur without any corresponding intestinal pathogenesis (Girges, 1934) and, conversely in Puerto Rico intestinal lesions are reported without any liver involvement (Pons 1937).

*S. haematobium* infection. The first symptom may be an irritating papular eruption in the groin, scrotum and/or perineum which goes on to pustular formation, but this may not be noticed by the less sensitive patient. The urinary symptoms usually do not appear until several months after infection took place and in some cases even several years. The first

come blocked as a result of peri urethritic inflammatory reaction to the deposited ova, and increasing difficulty in micturition alternating with incontinence will give place to complete suppression, or urinary fistulae may develop. Infection of the bladder soon becomes inevitable, and this in-

fection will spread to the kidney. There will be a return of fever, with emaciation and increasing weakness, soon followed by death.

In more chronic cases the polypoid growths in the bladder undergo malignant changes, and carcinoma of the bladder is a very common complication in Egypt.

Besides symptoms directly referable to the bladder involvement, the uterus and vagina may be involved in women and the penis in men, and there may also develop an elephantoid condition of the labia or scrotum, as a result of blocking of the lymphatics in the pelvis. A polypoid mass may develop around the anus, and the rectum may also be involved, with the development of fissures, fistulae and bleeding hæmorrhoids.

Acute appendicitis may result from deposition of eggs in the appendicular mucosa, but the latter incident, which is apparently very common in endemic areas, does not necessarily produce acute symptoms.

Bronchial asthma is a common result of schistosomiasis in Egypt and so also is interstitial pneumonitis.

In this infection, there are few symptoms referable to the liver, or spleen, but occasionally the ova reach other organs, as in the case of the other schistosomes, and may rarely produce symptoms.

#### DIAGNOSIS

This must be made (a) from the history of the patient, including past symptomatology, (b) from the clinical picture, including cystoscopy, sigmoidoscopy, and blood examination, (c) by immunological reactions, and (d) by the finding of the ova.

(a) *The history of the patient*—In the endemic areas, the fact of residing in these areas is the only sufficient presumptive evidence but this

of *S. hæma* In the case of even in *S.* obtained by sigmoidoscopic examination, pseudo-tubercles, sessile papillomata and pedunculated polypi and ulcers can be recognised, and from the latter, material can be obtained in which the ova may be found.

By digital examination of the rectum the abscesses and pseudo tubercles in the bowel wall and also in the posterior wall of the bladder may be felt.

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surrounded by areas of hyperæmia, hes. In the early stages of the in-

section, some information will be obtained from the blood picture. There are probably few diseases in which such a striking eosinophilia will be found, as during the early generalized reaction to the infection. On the other hand, many helminthic infections will cause a very marked eosin-

The intradermal test with a similar alcohol extracted saline antigenic preparation on the lines of the Casoni reaction in hydatid has been recommended, but it is not so reliable as the complement deviation test

(d) Finding of the ova in stools or urine—The parasitic diagnosis in many ways the most satisfactory, as it enables a definite diagnosis of the infecting species to be made but it will not be positive until the disease is well into the second stage, and there are advantages in an earlier diagnosis. Further, unless the ova in the stools are very numerous they are likely to be overlooked and some form of concentration method is advisable

Craig and Faust (*loc cit*) recommend a sedimentation method

ment in a conical  
ed the process is  
the miracidia will  
with a low power  
lens for the ova

An alternative method is to place the sediment in a tall glass cylinder full of water and leave it for 24 hours the ciliated miracidia will hatch out and can be seen by means of a hand lens swimming near the surface of the water

As indicated above, a more certain method of finding the ova is to take a swab specimen directly from the ulcer during a sigmoidoscopic examination

The finding of ova of *S. haematobium* in the urine presents less difficulty, if the urine is allowed to sediment in a conical glass, although they may only appear intermittently. In this infection also ova will sometimes be found in the stools

Thus to summarize, in the early stages a diagnosis must depend on the history, the clinical picture, and the complement deviation test, in the middle period cystoscopic or sigmoidoscopic examination and the finding of the ova in stools or urine will be additional methods and in the final,

the nature of the disease

#### PREVENTION

The reader is referred back to p. 714, where the essentials for the occurrence of the disease are given. No action can be taken under the fifth of these headings—climatic conditions, but each of the other four indicate



where the transmission cycle can be attacked. We will consider the subject under four headings which correspond to the first four essentials

(a) **The elimination of the source of infection**—The source of infection could theoretically be eliminated in the cases of *S. hæmatobium* and *S. mansoni* infections, by systematic treatment of the population as man is the only important source. This method will be less effective in the case of *S. japonicum* infection as there are other definitive hosts. In certain areas this method has been practised in conjunction with other procedures with some evidence of success as a means of reducing the source of infection but without any real expectation of eliminating it entirely.

The educational value of an organized treatment campaign is very considerable even the most ignorant natives of the endemic areas appreciate the value of treatment and are likely to take more notice of advice regarding prevention given by the doctors who can cure them.

The destruction of rodents and other possible alternative hosts of *S. japonicum* should be considered under this heading but the relative importance of these other hosts has not yet been properly assessed.

(b) **Destruction of molluscan intermediate hosts**—Theoretically this method promises well in practice except for isolated and limited bodies of water it has been a failure. Periodic drying of irrigation canals reduces the snails but some burrow in the soil and reappear later. The destruction of snails by chemical means e.g. 1 in 500 000 copper sulphate will lead to their temporary disappearance but unless the body of water is an isolated one rapid reinfestation will occur this has been the experience in Egypt.

For small isolated bodies of water when immediate snail elimination is required the introduction of copper sulphate sufficient to make a final solution of 1 in 200 000 to 1 in 500 000 should be applied this can be done by placing the copper sulphate in a bag and towing it behind a small boat backwards and forwards through the water preferably after preliminary removal of aquatic vegetation.

(c) **Prevention of contamination of water with human or other host's, faeces and urine**—All workers are agreed that this is the pivotal point of prevention but putting it into practice presents difficulties that are usually immediately insuperable.

In the endemic cases in Africa including North Africa and the Nile delta most of the population involved are ignorant peasants with not very high sanitary standards. In the dry parts of the country where there is little rain to wash surface contaminants into the waterways contamination of water must be deliberate and due to inappreciation of the significance of the act it should therefore be easier to prevent under these conditions than in wet countries where faeces and urine deposited promiscuously on dry land will frequently be washed into water.

The introduction of proper sanitary systems and education and propaganda are the only solution but it will be generations before they are fully effective.

Where domestic animals are sources of infection they should as far as possible be kept away from the vicinity of snail infested water.

In China, an additional problem has to be faced. There, human excreta are stored in *lang*s and later used as manure. If faeces and urine are undiluted with water, eggs will only survive in these *lang*s, which act as septic tanks for three weeks, so that if several *lang*s are kept and used in rotation and none is used within three weeks of the last addition of fresh faeces, the material should be free of eggs and miracidia. The addition of an antiseptic, such as sodium cyanide, that might add to the manurial value of the contents has also been suggested as a preventive measure.

(d) **Obviation of contact with contaminated water**—In the case of the individual foreigner, the knowledge of the local conditions and the knowledge of the necessary precautions are necessary. The specific endemic areas are not apparently penetrated by the skin under water, bathing in some antiseptic solution immediately on coming out of the infected water should prevent infection. Experimentally, it has been shown that cercariae go beyond the reach of alcohol applied to the skin within about ten minutes, so that any delay would nullify the effect of the procedure.

The case of the soldier or sailor under combat conditions is however different. Engineers who habitually have to spend a long time in the water (e.g. while building bridges) should be provided with high wading overalls, but these would be too cumbersome for the infantry. Data are not yet available, but it seems very probable that if the clothing were of a sufficiently fine weave, or if it were impregnated with copper sulphate

In the case of the native, his livelihood will often depend on entering water at frequent intervals, and prevention at this juncture of the transmission cycle seems to be out of the question. 'Nursery' rice fields are a very potent source of danger as these are heavily manured, as far as possible children, who are particularly susceptible to infection, should be kept out of these fields.

Under this heading must be considered the treatment of water that is to be used for household purposes. The cercariae will go through a 30-

In areas where some domestic animal, e.g. the water buffalo, acts as a reservoir of infection, every effort should be made to prevent such animals entering infected water to initiate or renew their infections.

#### TREATMENT

Treatment must be considered under two headings, specific and symptomatic.

### Specific Treatment

**History**—The first successful specific treatment was carried out by Christopher son in 1918 who at the suggestion of McDonagh, used intravenous tartar emetic that had been in use for several years in the treatment of leishmaniasis.

**Antimony preparations.**—The first drugs to be used were potassium and sodium antimony tartrate and many believe that even today they are the most effective. The sodium salt is apparently the less toxic. They are given in 2 per cent solution in normal saline made with distilled water. The solutions must be made freshly or some preservative, such as 0.5 per cent phenol, added in which case the solution can be kept at least two weeks. It is sterilized by being brought to the boiling point twice, prolonged boiling or autoclave. It is given three times a week. The dose should be increased to 3 c cm, 4 c cm, 5 c cm and 6 c cm, if the patient appears to be able to tolerate it. The principal signs of intolerance are coughing, vomiting, and joint pains. When these occur it may be necessary to increase the doses by only 0.5 c cm or even to repeat the last dose until tolerance is established. A total of at least 2 grammes should be the aim, which, if all goes well, will necessitate 18 injections over a period of 5 or 6 weeks.

Children are given proportionately smaller doses.

It appears to be necessary to push the dosage of this drug a little higher than in the case of kala-azar (*quod vide*, p 168). There is some difference in the tolerance of this drug by different nationals, Egyptians appear to tolerate the larger doses well, whereas in Venezuela the intolerance rate is high and it is sometimes necessary to drop the strength of the solution to 1 per cent.

Fouadin (or stibophen), a trivalent aromatic compound of antimony, is less toxic and also can be given intramuscularly. It is, in the experience of some workers, more effective than the pentavalent salts of antimony, but, in that of others, it has proved less effective. Fouadin is marketed as a 6 per cent solution in ampoules. The dosage is 1.5 c cm, 3.5 c cm, and 5.0 c cm, on the first three days, followed by 5 c cm, on alternate days until a total dose of 45 c cm, has been given (Khalil and Betache, 1930).

The latest recruit to the antimony preparations is the well-advertised but not very extensively tested, anthromaline—lithium antimony thiomalate (Baugé, 1941). Two cubic centimetres of a 6 per cent solution are given on alternate days, the course is 10 injections.

Emetine has also been recommended, but to be effective it has to be given in dangerous doses, it should therefore be reserved for those cases in which antimony has failed.

**Results of specific treatment**—The stage of the disease appears to be more important than the species of the infecting schistosome. The treatment will be effective only during the active stages of the infection, that is, before the third stage of the disease is established and irreparable damage has been done. In the earlier stages of the disease, the improvement is often immediate. The action appears to be on all stages of the worm including the ova, as the ova that are excreted after treatment has been well established are usually dead later, no more appear, indicating the death of the adult.

## Symptomatic Treatment

stages of hepatic involvement in the visceral infections, and such surgical procedures as appendectomy, splenectomy, and removal of polypoid growths

## PROGNOSIS

In the vesical infection the large majority of the attacks are mild and almost symptomless. In these and in all early cases the response to specific treatment is good, but in advanced chronic cases, when there is much involvement of the bladder wall and pelvic tissues, and when secondary infection has occurred, the prospects are poor and the patient will almost certainly die within a short time of sepsis or concurrent disease.

Similarly, in the visceral infections, there will be many symptomless infections. The course of the disease is on the whole slower and less severe in *S. mansoni* than in *S. japonicum* infection. In both, response to treatment in the early stages is good, but once the liver becomes cirrhotic, death within a year or so becomes inevitable. Even in the absence of liver cirrhosis, many patients with extensive bowel lesions will die of malnutrition and exhaustion.

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## OTHER FLUKE INFECTIONS

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## CLONORCHIASIS

**Historical**—This fluke was first discovered in the bile-ducts of a Chinese carpenter who died in the Medical College Hospital in Calcutta in 1874. It was described by McConnell (1875). The life cycle of the parasite was worked out by several Japanese parasitologists and the most important recent work on the subject was carried out by Faust and Khaw (1927).

## EPIDEMIOLOGY

**Geographical distribution**—The infection is endemic in China, Korea, Japan, Formosa and French Indo China. Its brief appearance in Hawaii was probably due to the consumption of fish imported from Japan.

**Incidence**—As the infection of man is dependent entirely on the consumption of under cooked or uncooked fish, the disease will be most prevalent in those groups of the population in which this practice is most common. In Canton for example, where fish is expensive, the disease is common amongst better class males who eat in restaurants where specially prepared class members eat in certain areas in certain parts of the city, the poor its

It is uncommon that symptoms due to this infection will occur in children on account of the time it takes for the pathogenesis to develop.

## ÆTIOLOGY

**The causal parasite**—Two phases of the parasite are likely to be encountered in man, the adult in the bile passages and the ova in the stools.

The adult of *Clonorchis sinensis* (Cobbold 1875; Looss 1907), is a semi-transparent leaf-shaped fluke measuring from 10 to 25 millimetres in length by 2 to 3 mm in breadth, slightly broader and more rounded at its posterior end.

The eggs are ovoid and flask-shaped with a distinct shoulder around the aperture over which the operculum lies. At the opposite pole there is a small knob or hook. The eggs measure 27 to 35 microns by 11.5 to 19.5 microns (figure 185). They contain a fully developed miracidium.

**Life cycle**—The ova are discharged in the faeces by the definitive mammalian host and are taken up by the intermediate host, a snail of the appropriate species, here the miracidium hatches out and the parasite

**Hosts.**—Man is an important definitive host and helps to maintain the cycle, but dogs, cats, badgers, weasels, martens, and minks and several other carnivora are also definitive hosts in nature

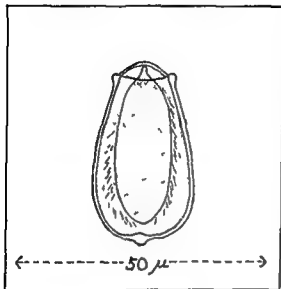


Figure 185 The egg of *Clonorchis sinensis*

Species of several genera of snails act as intermediate hosts, *Parafossarulus*, *Bithymia*, and *Melania*, and some 40 species of fish have been found infected

#### **PATHOLOGY**

The pathological reactions to the presence of these flukes appear to result from toxic substances secreted by the adult worms, from impaction of clumps of sticky eggs in small bile ducts, and possibly from mechanical damage by the adults themselves. All the primary changes occur in the liver, except in very heavy infections when the pancreas is

involved, all other pathological changes are secondary to liver damage

Fibrosis and thickening of the walls of the bile passages throughout the whole organ with proliferation of bile-ducts in certain areas, and both intralobular and interlobular cirrhosis are described. Hoeppli (1933) found extensive changes in 66 post mortem specimens from patients who died from other causes. (In view of recent work that has shown that extensive liver changes may result from dietary deficiency, it would be well to accept his conclusions as to responsibility of the parasite in all these cases, with caution.)

#### **SYMPTOMATOLOGY**

The majority of mild infections are apparently entirely symptomless.

The symptoms are not very characteristic and indicate liver damage generally rather than any specific damage caused by this parasite.

Gastro-intestinal disturbances are common, diarrhoea and irregularities of appetite, a sense of fullness in the liver region and liver enlargement, periodic jaundice, and later ascites, hæmorrhages and other results of cirrhosis often occur.

Cardiac and nervous symptoms are also described.

There is usually a leucocytosis and a slight eosinophilia.

## DIAGNOSIS

The only satisfactory method of diagnosis is by the finding and identification of the eggs in the stools. Flootation methods should not be used. Ova may also be recovered by duodenal catheterization.

## PREVENTION

Personal prophylaxis can be achieved by avoiding the consumption of under- or uncooked fish. Education and propaganda pointing out the danger of this practice in the endemic areas should be undertaken.

As man is an important source of infection, sanitary disposal of excreta is of great importance. In the absence of adequate sewage disposal, the excreta of infected persons should be disinfected with lime or other suitable agents.

A third method of control is by the destruction of snails (*vide* SCHISTOSOMIASIS) where this is possible.

## TREATMENT

There is no entirely satisfactory specific for this infection, but good results have been claimed for gentian violet (see p. 632). Other drugs used with apparent success are the antimony preparations, sodium antimony tartrate, and fousadin, and the gold preparation solganol-B.

## PROGNOSIS

The prognosis is generally good, but heavy infections undoubtedly cause irreparable liver damage and shorten the patient's life. In cirrhosis from whatever cause, the prognosis is bad.

Heavy infections undoubtedly cause irreparable liver damage and shorten the patient's life. In cirrhosis from whatever cause, the prognosis is bad.

## PARAGONIMIASIS

Paragonimus westermani is a lung fluke which is found in the lungs and other organs of man and various animals. It is found in the Far East, South America, and in the western hemisphere, in Peru, Venezuela, and Brazil.

Infection amongst mammals covers a much wider area including India, China, Japan, and various parts of South America. It is also prevalent in the Far East, South America, and in the western hemisphere, in Peru, Venezuela, and Brazil.

## ÆTIOLOGY

The causal parasite—*Paragonimus westermani* (Kerbert, 1878) Braun, 1899, is a relatively thick (3 to 5 millimetres) ovoid fluke, meas-



uring 7 to 12 mm in length by 4 to 6 mm in breadth slightly broader anteriorly than posteriorly with two suckers one placed at the anterior end and the other in the middle line slightly anterior to the centre of the body of the fluke

The eggs measure from 80 to 120 microns in length by 40 to 60 in breadth they are oval in shape and have a wide opening at one end over which there is a flattened operculum

The life cycle—The egg passed by the definitive host remains in water for several weeks before it is mature the time depends mainly on the temperature

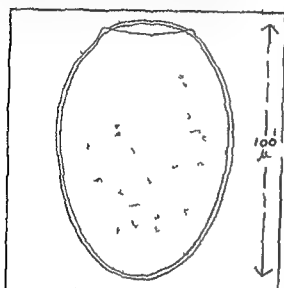


Figure 186 The egg of *Paragonimus westermani*

The miracidium emerges and enters a suitable snail after an interval of several weeks during which the parasite passes through several stages it emerges from the snail as a free swimming cercaria this cercaria actively enters the soft parts of a second intermediate host a crustacean and in this crustacean it encysts. When the crustacean is eaten by the definitive host (e.g. man) the metacercaria is released from its capsule by the time it reaches the duodenum it penetrates the wall of the duodenum migrates through the diaphragm and pleural cavity to reach the

lung\*. In a small pocket in the lung which is formed around the parasite it develops into an adult and when mature extrudes eggs that are coughed up by the host and the cycle is complete. If swallowed the eggs remain viable and are passed out with the faeces. The phase in the definitive host takes several weeks to complete.

Other organs or tissues in which the metacercariae may come to rest are the liver spleen brain peritoneum testes prostate epididymis muscles and skin.

**Hosts**—Besides man the tiger panther leopard wild cat domestic cat wolf fox dog mongoose muskrat and rat can act as definitive hosts.

*Melania libertina* is said to be the commonest snail intermediate host but *Ampullaria luteostoma* and other species of *Melania* are also potential hosts.

A number of crustaceans of the genera *Astacus* *Eriocheir* *Potamon* and others have been found infected and other crustaceans are probably capable of acting as the second intermediate hosts.

\* It is not clear why metacercariae should take this direct but somewhat unusual route rather than the more biological one via the lymphatics and systemic blood which would take them straight to the lungs.

## PATHOLOGY

In the lung there is a sharp cellular reaction to the presence of the parasite consisting mainly of polymorphonuclear leucocytes and eosinophils later, fibroblasts appear and eventually a thick band of fibrous tissue is laid down around the worm. Within this fibrous capsule besides the worm there is a mass of reddish brown purulent material in which the eggs of the worm can be found. Periodically these abscess like cavities communicate with an adjoining bronchiole and the fluid contents is discharged into a bronchus and coughed up or swallowed by the patient. The worm however remains and the process is repeated. Sometimes several of these cavities or tunnels coalesce and a comparatively large cavity is formed.

In other organs and tissues where the larvæ may come to rest and the adult worms develop a similar tissue reaction and 'abscess' formation occurs. In any of these places a secondary infection may take place and the fibrous capsule and its contents be replaced by an ordinary abscess.

## SYMPTOMATOLOGY

This will naturally depend on the main site of the encysted worms like that of pulmonary. There may be anæsthesia, paroxysms may occur. The reddish-brown sputum that the patient coughs up is suggestive of the rusty sputum of pneumonia. There may be a hæmorrhage after a particularly violent fit of coughing. In uncomplicated cases physical signs are few, but there are usually rales. However, complications such as broncho pneumonia pleurisy and empyema are not uncommon.

In the brain, the encysted parasites may cause Jacksonian epilepsy and other cerebral symptoms. In the liver, they may cause liver pain and enlargement, in the intestinal walls they may cause abdominal pain and gastro intestinal disturbances, in the prostate epididymes and testes, they may cause pain and swelling, and in the skin they may discharge at the surface and cause an open ulcer.

## DIAGNOSIS

This is dependent almost entirely on the finding and identification of the eggs, either in the sputum or in the stools. In the latter case they may have come from cysts in the intestinal wall that burst into the lumen of the intestine, or from the lung, having been coughed up and swallowed.

X-ray examination has proved disappointing as a diagnostic procedure.

A complement fixation test has given a high percentage of positive results.

## PREVENTION

It will be apparent from the ætiology of the disease that there are several points at which the transmission cycle could be attacked, but in none of these cases would it be possible to devise any practicable measures.

By means of education and propaganda and of necessary legislation, the practice of eating uncooked crustaceans should be stopped, but even this will not reduce the potential danger, as the cycle can probably be

maintained satisfactorily through other mammalian hosts, so that any future relaxation would probably again lead to the development of fresh cases

### TREATMENT

Practically the only treatment for which any success has been claimed is with emetine. Large doses, bordering on toxic doses, must be given

to be of any value. Doses of half a grain three times daily for at least a week have been recommended, and it is claimed that better results are obtained if this is combined with *prontosil* in full dose.

### PROGNOSIS

This is usually fairly good, except in the case of very heavy infections or in those cases in which serious complications have already developed.

### FASCIOLOPSIASIS

**Introduction** — This is a disease caused by the large intestinal fluke, *Fasciolopsis buski* (Lankaster, 1857), Odhner, 1902, that was first observed by Busk in 1843 in the duodenum of an Indian lascar who died in London. The pig is also a definitive host and probably the main reservoir of infection, the life cycle of this fluke includes stages in a snail and in an aquatic plant, and the fluke establishes itself in man when he eats the latter.

### EPIDEMIOLOGY

This infection occurs in India (Bengal and Assam), southern and central China, Indo China and Siam

Formosa, the Dutch East Indies and Borneo and other East Indian islands. It has not been reported from the other continents.

It occurs amongst the poorer members of the native populations of the endemic areas and mainly amongst children, who ingest the encysted embryos while they are removing with their teeth the outer covering of the edible portion of certain aquatic plants.

### ETIOLOGY

*Fasciolopsis buski* is a large broad hermaphroditic fluke, from 20 to 75 microns long by 8 to 20 microns across. It has one oral sucker at its anterior end. The eggs are large, 130 to 140 by 80 to 85 microns, golden brown in colour, and ovoidal in shape (see figure 187) (Plate A, fig 16).

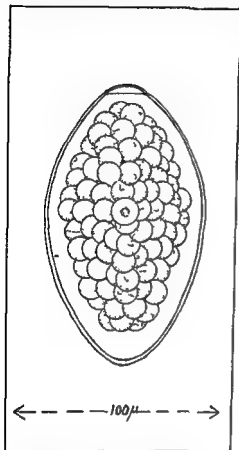


Figure 187 The egg of *Fasciolopsis buski*

The shell is thin and has a small operculum (a lid like structure) at one end. In the immature egg the contained protoplasm is divided into a large number of regular globular masses which almost fill the shell.

**Life cycle**—Man is infected by consuming raw aquatic vegetation, the parasite gaining entry in an encysted larval stage. Excystation oc-

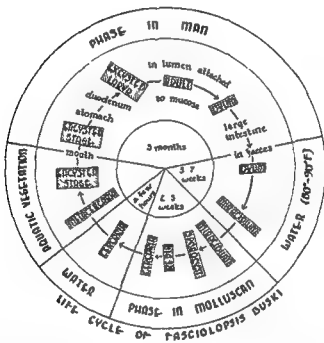


Figure 188

reaching the water mature in from three to seven weeks at a favourable temperature (80° F.-90° F). The miracidium that emerges from the mature egg swims for 1-2 days and then enters the soft tissue of a suitable snail. Genera have been found in a few weeks cercariae free swimming parasites they penetrate the seed pods and roots of certain aquatic plants where they encyst. In Bengal and Assam, *Trapa bicornis* and in China *T. natans* and the water chestnut *Ehocharis tuberosa* are commonly infected, these are ingested by man and the cycle is complete.

#### PATHOLOGY AND SYMPTOMATOLOGY

Within man the parasite lives only in the intestinal canal, but it is capable of causing considerable local damage to the intestinal mucosa at the point of its attachment. There is also evidence that it secretes a toxin

that is injected into or absorbed by the host. There is an area of inflammation around the point of attachment of the worm the centre of which later sometimes becomes necrotic, ulcerates, and bleeds, or an abscess may develop in the mucosa and eventually rupture into the intestinal lumen.

The fully-developed syndrome is that of a true dysentery, with severe abdominal pain, blood and pus in the stools, and considerable toxæmia and prostration. In heavy infections, particularly in children, the toxæmia predominates and is associated with œdema of the face, trunk and legs, and ascites, and may result in the death of the child. Milder infections will cause little more than abdominal discomfort, a toxic diarrhoea, and slight malaise, but even these mild infections eventually produce a state of malnutrition.

The blood picture usually shows a considerable eosinophilia with an absolute decrease in the other white cell elements, and a slight macrocytic (nutritional) anaemia, unless there has been much blood loss, when the picture may be confused by a microcytic tendency.

#### DIAGNOSIS

The diagnosis will usually depend on the finding of the characteristic eggs in the stools although after purgation the adults may be found. The eggs are almost identical with those of *Fasciola hepatica*, the sheep fluke that rarely affects man, and with those of *Echinostoma*, of which several species have been reported as parasitizing man occasionally.

#### PREVENTION AND TREATMENT

Consciousness of the mode of infection and a very modest degree of intelligence on the part of the potential victims are the only requirements for prevention. Abstinence from eating the incriminated aquatic vegetation is even unnecessary, as, if it is peeled without the aid of the teeth and well washed, infection will be avoided, for the cercariæ do not encyst in the edible portions. Immersion in boiling water for a few seconds should however be advocated as a safer procedure. In view of the simplicity of this method, discussion on other methods of breaking the cycle such as the destruction of snails and protection of the water courses from contamination, both of which will always be very difficult, would be purely academic. The latter would present insuperable difficulties in most endemic areas, as pigs are the main reservoirs of infection.

... tetrachloride, and hexyl  
used for other intestinal

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## HYDATID DISEASE

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pigs,  
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and other organs producing pathological changes mainly but not entirely by pressure. This disease occurs in temperate and cold climates principally where sheep raising is practised extensively, but it is also encountered in a few tropical and subtropical areas.

In view of the fact that it is in no sense a tropical disease and that it is usually dealt with adequately in standard textbooks on medicine and surgery, hydatid disease is only discussed summarily here.

**Geographical distribution**—Hydatid disease has an extensive distribution throughout the world, but the most important foci are Iceland, central and south eastern Europe, North and South Africa, South Australia, Tasmania, and New Zealand and Uruguay, Argentina and Chile. It also occurs extensively in Palestine, Syria, Arabia, and Iraq, and in Siberia.

In India the disease is comparatively rare, but perhaps not as rare as published reports would indicate (Editorial 1938) and there are undoubtedly isolated foci where a higher human infection rate exists (Samal 1938).

#### ÆTIOLOGY

**The causal organism**—*Echinococcus granulosus* is a minute worm 3 to 6 millimetres in length, consisting of a scolex, a neck, and one im-

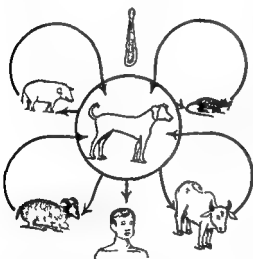


Figure 18° Showing the transmission cycles in hydatid infection

mature one mature and one gravid proglottid. It is an intestinal parasite of the dog, the wolf, the jackal, and rarely the domestic cat. The principal intermediate hosts are sheep, cattle, and pigs, but many other animals act as intermediate hosts, notably horses and camels. Man is infected sporadically, taking the place of an intermediate host in the infection sequence.

**The life cycle**—The egg which is indistinguishable from that of the *Tæniæ* is ingested by the sheep or other intermediate host. In the host's stomach the outer shell is digested off and the oncosphere emerges in the duodenum where it penetrates the intestinal wall to reach the mesen-

teric venules. It is usually filtered out in the liver but may work its way through these capillaries and even those of the lung to reach the systemic circulation and any organ or tissue of the body. Wherever it is held up it is either destroyed quickly by the tissue reaction or it develops into a hydatid cyst and commences to grow. Within this cyst brood capsules containing scolices develop. When the adult is mature the

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the uterus bursts discharging the ova into the bowel lumen to be passed out with the stools, or the detached proglottid itself may pass out of the intestinal canal before discharging the ova. Whichever happens, the cycle is now complete and the ova are ready to be ingested by another intermediate host.

It will be seen that man plays no part in the natural life cycle of the worm. His infection is incidental and the worms that infect him find themselves in a *cul-de-sac*, at least in all civilized countries.

### EPIDEMIOLOGY

There is evidence that climate *per se* has some influence on the distribution of the disease. For example, in Australia conditions are very similar throughout the country, yet it is only in the south that the disease is a serious problem and again it is difficult to explain entirely satisfactorily its relative infrequency in India although here there are undoubtedly other important factors besides the climate.

The disease is prevalent only in those countries where man, the dog, and sheep (or less commonly cattle and the pig) come into close association, and it occurs mainly amongst those members of the population that associate with dogs, e.g. farmers, shepherds and dog fanciers.

Whilst the diagnosis is often delayed until late middle life this is because the hydatid takes many years to reach clinical proportions when it is located in some non-vital structure such as the liver and it is believed that many, or possibly most, infections occur during childhood. The eyes are affected equally.

**Factors in the infection of man**—From the point of view of man, sheep and other domestic—and possibly also wild—herbivores are the reservoirs of infection and dogs—primarily, and to much less extent other carnivores—are the vectors. The two primary factors in the infection of man are

- (i) The infection rate amongst dogs.
- (ii) The number of dogs in a locality (a) that may be directly associated with man (b) that may contaminate man's water or food and (c) that may contaminate sheep and cattle pastures.
- (iii) The closeness of (a) the direct association between dogs and man and the extent of the opportunity for the former to contaminate (b) man's food or water and (c) sheep or cattle pastures.

The secondary factors on which the infection rate in dogs will depend are

- (iv) The number of infected sheep or other domestic or wild herbivores in the locality, (in sheep 90 per cent of the hydatid cysts are fertile against 88 per cent of those of other herbivores (Peres Fontana 1936) so that the former are far more important).
- (v) The opportunities that dogs enjoy of feeding on the viscera of herbivores.

The subject could be discussed briefly under each of these headings.

(i) In many countries, the infection rate amongst dogs is very high, up to 50 per cent (South Australia), whereas in others (U.S.A.) canine infection is almost unknown (Sawitz, 1938). There is a rough parallelism between canine and human infection but the human infection rate is nearly always on a much lower plane. At one time in Iceland where infection rate amongst dogs was 30 per cent, it was stated that nearly 20 per



cent of the population was infected, whereas in countries where infection in dogs is rare, e.g. the United States and Canada, only 29 autochthonous cases have been reported in over a hundred years (Magath, 1941)

For India, only two reports need be quoted, Sami (*loc cit*) found 89 per cent of 89 dogs infected in a rural district in the Punjab where he reported 40 human cases seen in a period of five years, whereas Maples (1933) found only two infected out of 100 dogs examined in Calcutta where the human disease is undoubtedly rare

In Iraq, Senekj and Beattie (1940) found 17.8 per cent of 123 dogs infected

The infection rate in dogs will depend on factors (iv) and (v)

(iv) The disease is generally more common in countries and among communities in which there is a high proportion of dogs to human beings. In Uruguay, Perez Fontana (*loc cit*) reports a ratio of dog man = 2.1 houses where hydatid disease occurs, against 1.8 in the general community

(v) (a) The question of direct association between man and dogs is a matter of practice, to which it is impossible to attach figures. Where dogs are important as draft animals, as in Iceland and other cold countries, or where they are an important part of the farm personnel, as sheepdogs, they are treated almost as human beings and given free access to the living and sleeping quarters (a modification of this practice has caused a recent reduction in the incidence of the disease in Iceland). In many other instances, children are allowed to play freely with dogs. Even in certain eastern countries, e.g. amongst the Hindus in India, dogs are looked upon as unclean animals and are allowed to exist as outside scavengers only. This is the important factor in determining the high incidence of the disease in the former communities e.g. Iceland and New Zealand and the comparative rarity in others, e.g. India

(b) The indirect association by contamination of drinking water and food supplies of the population may obviously be a danger in some countries, but it has never been given an important place as a cause of the disease

(c) The chances of the infection of sheep, cattle and pigs from the promiscuous defecation of dogs in pastures will be a constant danger and will depend mainly on the numbers of uncontrolled dogs that there are in any locality, and the proximity of the pastures to the village, away from which the dogs seldom stray any distance, except those that are used for herding cattle

In these instances the infection rate is 7 to 10 per cent. Near East (Senekj & Beattie (1940)) 17.8 per cent in cattle. On the other hand, in India the infection rate in sheep and cattle was sometimes also high. In Calcutta the writer could always obtain several hydatid livers any day by visiting a slaughter house and in the United States it is far from negligible, but for reasons given here the incidence of hydatid disease is not high in either of these countries. The infection amongst domestic herbivores is probably maintained by cross infection from wild carnivores and herbivores (Riley, 1933)

(1) In many countries (*e.g.* in South America and New Zealand) dogs have in the past been allowed to feed on the livers of slaughtered sheep especially those that were diseased and therefore of no value. This practice has declined as a result of propaganda as well as because of the economic fact that liver is now more valuable. In the United States, slaughter houses are better controlled, so that the incidence of infection amongst dogs and thence amongst human beings, is low. The higher commercial value of entrails in India has also been a factor in keeping the infection rate in dogs at a comparatively low level in most parts of the country. In that country the low association index between man and dogs and the climate, already mentioned, are also factors.

### PATHOLOGY

The pathogenesis is caused by, (i) the pressure of the growing parasite, (ii) the seeping through the capsule of small quantities of allergins and toxins, (iii) the rupture of an hydatid cyst with the sudden release of large quantities of hydatid fluid containing allergins toxins and daughter cysts into the blood stream, a serous cavity, the lung, or a hollow viscus, (iv) the development of secondary cysts in other organs and tissues and (v), as a common complication the infection and suppuration of an hydatid cyst.

**Distribution of the lesions.**—When the onchospheres find their way into the portal circulation the first organ that they reach will be the liver, about three-quarters of the hydatid cysts recognized clinically or post mortem occur here, of which four out of five are in the right lobe. Some will work their way through the liver, and of these roughly half will be held up in the next set of capillaries that are in the lungs about 10 per cent of hydatid cysts are found in the arterial blood and are at other sites, roughly in the order of tissue bone muscle, kidneys. The high percentage reported as occurring in the peritoneum are certainly mainly due to metastases from a ruptured primary hydatid.

**Development of the hydatid cyst.**—Of the onchospheres that come to rest in the various organs, most probably the majority are destroyed by the tissue reactions those that survive develop into hydatid cysts and grow, reaching a size of 250 microns in about three weeks. They are now surrounded by a characteristic tissue reaction, immediately around the cyst are endothelial cells and giant cells, which are surrounded by a layer of fibroblasts with new capillary formations and infiltrating eosinophils, and an outer layer of denser fibrous tissue. When a cyst is located in the liver or other organ it may be found in a man the attain the zable clin-

As the cyst grows, its outer covering becomes thicker and less permeable so that tissues in which it lies react less specifically but rather as they would to any foreign body. The mature cyst consists of three layers, one of host and two of parasite.

slight tension in which will be found 'hydatid sand', consisting of brood

**Exogenous budding** also occurs—In such cases the tumour develops a much more 'malignant' character, as it invades rather than compresses the surrounding tissue and eventually a large multiloculated cyst which may involve practically the whole liver will result. Also without rupturing it may give rise to metastases. (It is a matter of controversy whether this exogenous budding is not the characteristic of a different species or strain of echinococcus. The evidence for this is that it commonly occurs only in a few geographical localities, *eg* in Central Europe, but the present consensus is that there is only one species and that some special condition determines its special development.)

When the cyst grows within the skull or the spinal column, it naturally

like that of cystic disease of the bone, there is rarefaction of the bone and spontaneous fracture is likely to occur.

**Spontaneous rupture**—This is not an uncommon incident. Hydatids of the liver usually rupture into the peritoneum, or into the gall-bladder or bile ducts. In the former case, the only immediate result may be shock and allergic manifestations, but after several years a large number of cysts may develop in various parts of the peritoneal cavity. In the latter, the daughter cysts may cause a temporary blocking of the common bile duct, but the more serious consequence will be the almost inevitable infection of the cyst cavity.

In the lung, rupture into a bronchus is not uncommon. If the cyst is a large one, the incident may drown the patient, but, if he survives this, the prognosis is usually good.

**Suppuration**.—This may occur in any cyst, but in the case of a unilocular cyst it is usually the result of a leak or rupture into a hollow viscus. The suppuration rate amongst multilocular hydatids is much higher than amongst the unilocular cysts.

The changes that occur when hydatid cysts develop in other, rarer locations need not be discussed here.

**Calcification**.—When a hydatid cyst dies, the fluid will be absorbed slowly and be partially replaced by caseous matter. The cyst wall shrinks and may become calcified. What remains of the cyst is now completely surrounded by fibrous tissue, and causing no further symptoms is perhaps discovered *post mortem*.

#### SYMPTOMATOLOGY

**Latent period**.—After infection it will usually be from five to twenty years before the first symptoms appear, and it has been estimated that in about 25 per cent of cases the cyst remains symptomless throughout life.

**Onset and course**.—The onset of symptoms may be very gradual, or it may be sudden, either due to the bursting or suppuration of a hydatid cyst. It will be appreciated from consideration of the pathology of the condition that the nature of the symptoms in either case will vary accord-

ing to the site of the cyst and in the latter according to the direction in which it bursts

the patient will immediately suffer from shock and possibly an urticarial rash a little later, after which there may be another latent period of five to ten years before the secondary hydatids in the peritoneum begin to cause symptoms. Or, if it bursts into a bile duct there may be biliary colic and obstructive jaundice and later suppuration with pyrexia and other complications associated with a liver abscess. If it bursts into the pleural cavity, from the liver or from the lung after initial shock the signs will be those of pleurisy with effusion.

Multilocular or alveolar hydatids on account of their invasive nature more readily become infected so that irregular pyrexia and pain suggestive of hepatitis or liver abscess will occur without definite rupture.

be asphyxiated by the fluid and the daughter cysts obstructing the bronchi or he may be able to cough up the contents. In such cases about 75 per cent recover spontaneously but in others a lung abscess may develop.

In the brain, the pressure symptoms will usually appear earlier but at first they may amount to little more than headache and visual disturbance and the hydatid may reach a considerable size—demonstrable by x ray—before the more serious signs and symptoms of intracranial pressure cause a diagnosis of tumour to be made. Again everything will depend on the localization. Sudden death may occur from pressure on vital areas or rupture of a cyst into one of the ventricles.

In the bones, pain will usually be the first symptom later there may be deformity and spontaneous fracture.

In the kidney, the condition will be suggestive of a hydronephrosis or a tumour. Similarly, in other organs and tissues the symptoms will be those of a benign tumour, and when it is palpable of a cystic tumour.

### DIAGNOSIS

This is a matter of very great importance as even in countries such as Australia and New Zealand where the disease is common only about half the cases reported are diagnosed pre-operatively and for proper treatment accurate diagnosis is essential. Diagnosis can be considered under six headings—

(i) **Clinical**—The only pathognomonic finding is a 'hydatid thrill', which can be felt in the cyst.

with the minimum of general or local effects



(c) The reduction of the direct association between dogs and man this can be done by reducing the number of dogs as above but also by

- (i) keeping dogs out of the houses
- (ii) not allowing them to lick out plates or other utensils used by man
- (iii) avoiding the fondling of dogs and
- (iv) forbidding children from playing with dogs

These measures against dogs are particularly applicable in countries where there is a high percentage of infection amongst dogs. In other countries, the precautions might be relaxed regarding individual dogs that are known by careful and repeated examination of their stools to be uninfected and that are kept under proper control so that their chances of access to infected material are minimal.

Some of these measures can be aided by suitable legislation but education and propaganda will be essential to achieve success in the prevention of this infection. Already a very considerable degree of success has been achieved in Australia and New Zealand and also in Iceland.

#### TREATMENT

No drug has yet been found that has any specific effect on the parasite in the stages in which it occurs in man. It seems very possible that a specific might be found that would destroy the parasite in its early stages but it would be difficult to establish its efficacy and its practical use would be limited to the periodic administration to those under serious risk, however, even in such cases other preventive measures would be preferable. The insulation of the cyst by the thick fibrous capsule that occurs in its later stages makes it problematical if a drug will ever be found that will penetrate the cyst and destroy its contents. Treatment must therefore be expectant or surgical.

**Surgical**—It will naturally depend on the location of the hydatid whether this is possible or not. Hydatids of the liver are those that call for surgical treatment most frequently. The aim must be to remove the contents and the parasitic layers of the cyst and to close the cavity as far as possible, without open drainage. This must be done without any contamination of the peritoneal cavity with the hydatid fluid.

It would be out of place to describe the surgical procedures in detail. The cavity is washed out with saline solution, the contents are removed, the cavity is washed out with iodine solution, the daughter cysts and scolices, cutting down on and shelling out the parasitic layers of the cyst, and again swabbing out the cavity with 10 per cent formalin.

#### PROGNOSIS

Hydatid disease is always a serious condition but its seriousness depends very largely on the location of the cyst and when operative treatment is undertaken, on the experience and skill of the surgeon. In the hands of a skilled surgeon, the immediate prognosis in unilocular liver hydatids is good, but recurrences in the peritoneum still occur in a considerable percentage of cases. The prognosis in multilocular and suppurating hydatids is bad.

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## NORMAL DIETETIC REQUIREMENTS

**Introduction**—For growth and repair of the human frame and for the production of energy, a certain quantity of food is necessary. The three



energy-producing principles of food are protein, fat, and carbohydrate but there are a number of other essential nutrient elements, for example, minerals salts, the most important of which are those of iron, calcium and phosphorus, and the vitamins, water is also essential. The food requirements of man have been studied very extensively, although it would be absurd to suggest that there was not a very great deal more to be learned. The energy value of different food substances and the energy requirements of the organism can be estimated. The unit of expression

usually called, and a gramme of fat will produce nine calories of energy (or heat). Although the calorie value of the mineral salts and vitamins is negligible, they are essential for body-building purposes and for the proper utilization of the energy-producing foods.

**Calorie Requirements**—The calorie requirements of man vary according to the age and size of the individual, as well as the type of work that he or she is doing. There are formulae for calculating calorie requirements dependent on weight and body surface, but for practical purposes it is usual to take a 'basic' calorie allowance, to apply coefficients for individuals of different ages and for special conditions such as pregnancy.

TABLE XIX\*

Work		Supplementary allowance	
Light work		75 calories per hour of work	
Moderate work		75—150 calories	
Hard work		150—300 calories	
Very hard work		300 calories upwards	
Age in years		Coefficient	Calories
1—2		0.35	840
2—3		0.42	1000
3—5		0.5	1200
5—7		0.6	1440
7—9		0.7	1680
9—11		0.8	1920
11—12		0.9	2160
12—15†		1.0	2400
Males 16 upwards		1.0	2400
Women not pregnant		0.9	2160
Women pregnant		1.0	2400
Women lactating		1.25	3000

It is not uncommon to apply the coefficient of 0.9 as a maximum to women, except of course pregnant and lactating women. For babies under the age of one year, the calorie requirements are best supplied on a body-weight basis, thus—

Under six months	100 calories per kilogramme or 45 calories per pound
Six months but under one year	90 calories per kilogramme or 41 calories per pound

\* Recommended by The Technical Commission for the Study of Nutrition of the Health Organization of the League of Nations (1936)

† Meets needs of puberty

An allowance will also have to be made for the muscular activities of children, this is usually calculated as 75 calories per hour of active play

be roughly

Protein   Fat   Carbohydrate=1 1 5

It is, however, essential for purposes of body building that a diet should include a sufficiency of good protein.

The composition of all common foodstuffs in terms of protein, fat and carbohydrate has been worked out and can be read from the many tables that have been prepared, these tables usually give the calorie value of a given weight of the substances but, if they do not, this can easily be calculated from their composition. Table XXIV at the end of this chapter, which supplies these data for certain common foodstuffs is given as an example only. Workers in tropical countries should always obtain dietary tables for the common foodstuffs of the country in which they are living, in India, for example, from *Health Bulletin No 23* (Aylroyd 1940).

**Protein Requirements.**—The protein intake of an adult should not be less than 1 gramme per kilogramme (or 0.45 grammes per pound), but the requirements of growing children are proportionately very much greater, the amounts shown in the following table are recommended

TABLE XA

Age in years	Protein requirements in grammes per kilo of body-weight
1-3	3.5
3-5	3.0
5-12	2.5
12-15	2.5*
15-17	2.0
17-21	1.5
21 upwards	1.0
Women pregnant 0-3 months	1.0
" 4-9 "	1.5
lactating	2.0

Protein is built up from chemically simpler substances, amino-acids. During metabolism these are absorbed and re-arranged as body proteins. There are about twenty-two different amino acids, some ten of which

children and pregnant or lactating women

Fat Requirements for the dietary element considerably with the c is often given as the c

- Meets needs of puberty

and 60 grammes. Perhaps more important is the nature of the fat, and at least half should be of animal origin. A function of fat is its vitamin-carrying capacity and fats of animal origin are on the whole a richer source of vitamins, however, perhaps more important, fat dissolves and increases the absorption of the fat-soluble vitamins. Further, certain unsaturated fatty acids, e.g. linoleic and arachidonic acid, appear to be essential dietary elements.

**Carbohydrates.**—These are the main sources of energy, and except under starvation conditions are more likely to be taken in excessive than in deficient quantities. They are the main constituent of cereals and root vegetables, and sugar consists solely of carbohydrates.

**Mineral Requirements.**—Very small quantities of these are required but the minimum requirements have been calculated.—

**Calcium:**—Fish, milk, eggs and vegetables are rich in calcium. Cereals, especially rice, are poor sources, whole meal is, however, a moderately good source.

The daily requirement of an adult is about 0.7 grammes, but that of a child, who needs an excess of calcium for bone formation, is at least 1.0 gramme, of a pregnant woman 1.5 grammes, and of a lactating woman 2.0 grammes.

**Phosphorus.**—This is seldom deficient in any diet adequate in calories and other essentials. It occurs in most food substances and cereals are a rich source of phosphorus, some will be lost in washing and cooking.

**Iron.**—This occurs in many foods, in cereals, pulses (legumes), fruit, vegetables, and meat, especially liver, but it is present in negligible quantity in milk. Iron is not however assimilated from the food quantitatively, in some foods most of the iron is 'available', that is to say, easily assimilated.

older  
liable  
food  
with  
that  
It  
loss,  
e.g.

hookworm infection and hæmorrhoids, that there may be a relative iron deficiency, even in persons on a good diet. The infant is born with about 0.5 g. of iron, which is lost when a pure milk diet is given.

...

...

The daily iron requirements of the adult have been placed at 12 milligrammes, but in criticizing a diet one should expect at least 20 milligrammes to allow for some of the iron not being 'available'. A far better indication of iron deficiency in a population will be obtained by blood examination than by a diet survey.

A hypopopulation in which there is a high percentage of schistosomes will almost certainly show an anaemia, even in the absence of iron deficiency. This will suggest that the iron intake is low, and relatively inadequate.

...

It will seldom be worth modifying the diet to any extent on account of iron deficiency, it will nearly always be more economical to give additional iron medicinally.

**Fluorine**—This is an essential dietary element. Its absence during the period of formation of the teeth appears to lead to early dental caries, and there is some evidence that fluorine present in sufficient quantities (1 part per million) in the drinking water taken in later life will protect the teeth. The requirements have been placed at 0.5 milligrammes *per diem*.

On the other hand, excess of fluorine in the water will lead not only to band formations and mottling of the enamel of the teeth but to changes in the bones, for example the development of exostoses that may result in the ankylosis of the joints, of the spinal cord, or of the thoracic cage, and eventually to the death of the patient from secondary infection. Amounts

**Copper, iodine, manganese and other minerals**—Iodine will only be deficient in certain countries or parts of countries where iodine is absent from the water. In such countries special arrangements have to be made for supplying iodine medicinally at intervals throughout the year or in some domestic food ingredient such as salt, in order to prevent goitre.

Of the other minerals, there is always sufficient in almost any diet to supply the minimum requirements.

**The Vitamins**—Important as they are, the vitamins have received far more attention than their relative importance warrants on account of the wide advertising of vitamin preparations to both the medical profession and the laity during the last decade. It is not very often that a

special circumstances such as war  
not obtainable

Medical attention was first drawn to the vitamins by certain clinical syndromes that were traced to the gross deficiency of specific vitamins (e.g. beri beri, due to deficiency of vitamin B<sub>1</sub>, scurvy, due to deficiency of vitamin C, and rickets, due to the deficiency of vitamin D). Far more important however are the widespread minor degrees of ill health that are attributable to lesser degrees of deficiency.

In the determination of pathological processes associated with vitamin deficiencies, it is obvious that there are other factors than the actual amount of the vitamin in the diet or even than the amount absorbed, amongst a group of persons on more-or-less the same diet deficient in a particular vitamin some will show the gross deficiency and others will not. While yet factors, so

Amongst these factors are, (a) other dietary substances taken (e.g. large amounts of any vitamin-free cereal appear to increase the requirements

TABLE XXI

Summarized Data on Important Vitamins

Vitamin	Names	Solubility	Sources	Stability	Physiological action	Average adult daily requirements	Pathological effect of deficiency
						International unit	milligram
A	Anti-infective Carotene pro-vitamin	Fat-soluble	Green vegetables, carrots, butter, liver, some fruit, eggs and red palm oil	Prolonged heating destroys	Essential for cell growth and replacement especially affects epithelial tissues. Precursor of visual purple.	5000	300
	Thiamin Anserin	Water-soluble	Yeast, unmilled cereals, nuts and vegetables, some fruits, glandular organs, meat (Milk is poor source and milled cereals very poor)	Heat-labile with alkalis and 100°C acid sol	Controls carbohydrate metabolism by catalyzing of pyruvic acid	330 to 660	1-2
B complex	Riboflavin	Water-soluble	Pulses, milk products, liver, eggs, meat, some green vegetables and tubers, yeast (Marmite)	Heat-stable	Factor in enzyme system that regulates cell oxygenation and affects protein and carbohydrate metabolism		2 to 3
	Nicotinic acid Niacin	Water-soluble	Meat, liver, yeast, whole cereals, pulses, carrots, pulses (Milk is poor eggs a negligible source)	Heat-stable	Same as Riboflavin and may also affect water and iron metabolism		20
C	Ascorbic acid	Water-soluble	Citrus and other fruits, hips and berries, amaranth, green vegetables, tomatoes, potatoes (Little in human milk, less in cows)	Heat-labile in presence of oxygen	Formation of collagen and intra-cellular cement substances, detoxication	1000 to 2000	50-100 Adults 1-2 Child 3-8 Pregnancy 8-10 per kilo
D	Calciferol	Fat-soluble	Fish liver oils, fish, eggs, milk and butter of pastured-fed cattle. Action of sunlight on subcutaneous fat	Heat-stable	Balance calcium and phosphorus absorption and execution bone formation	400 to 800	Rickets, osteomalacia and osteoporosis, failure of calcification
E	$\alpha$ -tocopherol	Fat-soluble	Seed germ oils, e.g. wheat and rice germ, lettuce, alfalfa	Heat-stable in absence of oxygen	Directs activities of cell nuclei, affects cell differentiation and division		6
K	Pro-thrombin factor	Fat-soluble	Alfalfa, spinach, cabbage, kale, cauliflower, soy-bean oil, egg yolk, liver, milk and eggs (a little), bacterial putrefaction of macro-organism	Heat-stable	Pro-thrombin formation		1 to 10

Haemorrhage of the new born  
Hemorrhagic catarrhes in  
obstructive jaundice and  
liver disease

of vitamin B<sub>1</sub>) (b) infections (e.g. wound sepsis, which similarly appears to increase the requirements of vitamin C), (c) endocrine deficiencies (*vide infra*, myxœdema and pellagra), and (d) the personal factor (an expression that is a cloak for our ignorance). Again, vitamin deficiencies are seldom single, for, if a diet is deficient in one vitamin, it will usually be deficient in one or more other vitamins, especially in those found in the same food stuffs. Examples of grouped deficiencies are the fat-soluble vitamins A and D, and the water-soluble B vitamins respectively.

to be found in large and small amounts and what diseases and minor disabilities their deficiency causes but in many instances we know their chemical formulæ and the exact daily minimum requirements of the human organism. The writer does not propose to discuss the various vitamins in any detail here but only the special dietetic problems that are likely to face the worker in the tropics. The reader who is not familiar with this important subject is advised to refer to one of the many standard textbooks on dietetics, but in order to help him to follow the subsequent discussion on the dietary deficiencies encountered in the tropics a table giving summarized data on the important vitamins is appended (see Table XXI).

#### DIETETIC REQUIREMENTS IN THE TROPICS

The basic dietary requirements in the tropics are naturally very much the same as they are in temperate climates at least qualitatively but it has been found that quantitatively certain reductions should be made. Arkroyd (1941) considers that the caloric requirements of the average male adult Indian for example engaged in a sedentary occupation is 2 100 calories or 10 per cent less than that of the average native of temperate western countries to this he adds 450 calories for the light to moderate work in which the average agriculturist is engaged making a total 2 600 in round figures. To this figure he applies the following coefficients —

TABLE XXI

	Coefficient	Calories required (to nearest 100)
Adult male (over 14)	1.0	2 600
Adult female (over 14)	0.8	2 100
Child 12 and 13 years	0.8	2 100
Child 10 and 11 years	0.7	1 800
Child 8 and 9 years	0.6	1 600
Child 6 and 7 years	0.5	1 300
Child 4 and 5 years	0.4	1 000

For pregnant women he allows 2 400 calories and for lactating women 3 000. For those engaged in heavy manual work a further allowance must be made on the lines of the allowances made for hard work in temperate countries (*quod vide*).

**Protein** — Vegetable proteins are as a rule poorer than animal proteins (the natives of the tropics are on religious or economic protein in their diets). As a rule, at least one third of the protein should be of animal origin and for growing children and pregnant and lactating women the proportion should be higher. It will be seen from the table of biological values of

protein that, even if meat is taboo, milk and eggs can be taken to provide protein of high biological value

**Fat.**—The fat requirements are certainly less than in temperate climates. A diet containing 50 grammes of fat need scarcely be considered

*guineensis*) oil which is rich in vitamin A, this palm grows in Malaya, Burma, and West Africa, whence some is exported to other tropical countries, but little of this oil is consumed in India or China. Other vegetarian foods that are rich in vitamin A are nuts and soya beans.

**Mineral salts and vitamins.**—There is no satisfactory evidence, except possibly in the cases of vitamin B<sub>1</sub> and choline, that the requirements of these are in any way different from those in temperate climates. However, the blood depletions of parasitic infections, more common in the tropics than elsewhere, make the average iron requirements greater than in the temperate zones, and, conversely, the oral vitamin-D requirements are

**Some tropical dietaries.**—Data from several tropical countries are available, but India, with its four hundred million inhabitants and its varied climatic conditions and racial types, provides a sufficiently wide variety of diets to form the basis of a discussion on tropical dietaries. India has possessed an efficient nutritional research unit for about twenty years. This was started by Sir Robert McCarrison under the auspices of Indian Research Fund Association and for the last 8 years has been ably directed by Dr. Coonoor. The dietaries of many of the countries from a point of view

It has been found that the diet of the poor rice eater is much the same all over India. It consists of pulses and daily non-vegetarian food. The amount of milk is usually negligible. The diet is deficient in protein and vitamins.

described above

In about 30 per cent of the surveys which were carried out in widely separated areas the average calorie intake was below 2300 per consumption unit, below any reasonable standard of requirements. Again within certain groups some 30 to 40 per cent of families were not obtaining enough food. While it is not justifiable to apply these results to India as a whole there can be no doubt that a high percentage of the population is habitually underfed and the extent of under-nutrition is of fundamental importance. Enough food takes precedence over the right kind of food and to produce more food must be the foremost aim of agricultural policy.

Intake of total protein is usually sufficient when the calorie yield of the

TABLE XXIII  
Some Indian Diets  
(Ounces per consumption unit\* per day)

Food	1	2	3	4	5	6
	Assam Tea plantation labourers	Madras Beriberi area Villagers.	Orissa Villagers	Bihar Well-paid industrial families.	Central Provinces Villagers.	Punjab Villagers.
Rice	19.0 (home-pounded and milled parboiled)	21.5 (mostly milled raw)	24.6 (home-pounded parboiled)	21.0 (milled parboiled)	1.5	none
Wheat	none	none	none	none	none	17.4
Millet	none	none	none	none	16.0†	none
Pulses	1.0	0.3	0.2	3.4	2.0	1.9
Leafy vegetables	0.2	0.4	0.3	0.1	none	4.6
Non-leafy vegetables	3.4	2.9	7.7	6.2	4.5	2.5
Fruit	none	0.2	none	0.9	none	negligible
Vegetable oils	0.3	1.3	0.1	1.8	0.2	1.2
Onion	none	negligible	none	(mostly ghee)	none	8.7
Milk and buttermilk	0.5	1.0-2.0	none	3.7	1.8	none
Meat, fish and eggs	0.2	0.1	1.1	1.6	0.1	none
Sugar and jaggery	negligible	0.1	none	0.5	negligible	not reported

1 Wilson and Mitra. (1938)

2 Nutrition Research Laboratories (unpublished)

3 Narindra Singh. (1939)

4 Mitra. K. (1940)

5 Nutrition Research Laboratories (unpublished)

6 Ahmad and Gore (1933)

\* A consumption unit is the allowance for one male adult. Any additional male adult members are counted as one unit, and other members according to the coefficients shown in Table XXIII above.

The populations of which the average diets are shown in the above table are normal populations, none of these surveys was taken in a famine area, nor was any particularly poor population, of which there are many in India, included. In his invaluable *Health Bulletin No. 23*, Dr Aykroyd (1941) gives an example of the type of poor and ill balanced diets that is often encountered in India, this is shown diagrammatically in figure 190 in which a balanced diet suitable for an Indian peasant of a rice growing district is also shown. An analysis of these two diets is given in the table below.

TABLE XXIV  
Summary of an ill-balanced and a well-balanced diet

Constituent	Amount in ill-balanced diet	Amount in well-balanced diet
Protein in grammes	33	73
Fat "	19	74
Carbohydrate "	357	408
Calories "	1750	2500
Calcium "	0.16	1.02
Phosphorus "	0.60	1.47
Iron in milligrammes	9.00	41.00
Vitamin A international units	500	7000
" B <sub>1</sub> "	160	400
" C, in milligrammes	11	17



protein that even if meat is taboo milk and eggs can be taken to provide protein of high biological value

**Fat**—The fat requirements are certainly less than in temperate climates. A diet containing 50 grammes of fat need scarcely be considered deficient in fat and one containing the classical 100 grammes will usually be too rich for either the natives or the Europeans.

ever it is imp-

because some

very poor in vitamin A. An exception to this rule is red palm (*Elaeis guineensis*) oil which is rich in vitamin A, this palm grows in Malaya, Burma and West Africa whence some is exported to other tropical countries but little of this oil is consumed in India or China. Other vegetarian foods that are rich in vitamin A are nuts and soya beans.

**Mineral salts and vitamins**—There is no satisfactory evidence except possibly in the cases of vitamin B<sub>1</sub> and choline that the requirements of these is in any way different from those in temperate climates. However the blood depredations of parasitic infections more common in the tropics than elsewhere make the average iron requirements greater than in the temperate zones and conversely the oral vitamin D requirements are usually less on account of the longer periods of sunlight to which people are subjected in the tropics (see p. 764). Iron cooking vessels are often used in the tropics and this probably helps to meet the demand for iron.

**Some tropical dietaries**—Data from several tropical countries are available but India with its four hundred million inhabitants and its varied climatic conditions and racial types provides a sufficiently wide variety of diets to form the basis of a discussion on tropical dietaries. India has possessed an efficient nutritional research unit for about twenty years. This was started by Sir Robert McCarrison under the auspices of Indian Research Fund Association and for the last 8 years has been ably directed by Dr W. R. Aykroyd who in his nutrition laboratories at Coonoor and elsewhere has carried out a systematic investigation of Indian dietetics as well as much research work arising therefrom and has in many aspects of a lead to other tropical countries. The Indian dietaries are taken from a paper by

It has been found that the diet of the poor rice eater is not the same as that of the well-to-do. The diet of the poor is deficient in protein and fat, and is lacking in many of the essential vitamins. The diet of the well-to-do is more varied and contains more of the essential nutrients. The diet of the poor is also deficient in iron and calcium.

described above

In about 30 per cent of the surveys which were carried out in widely separated areas, the average protein consumption was below 2300 per consumption unit.

Again, within certain groups some are getting enough food. While it is not true that there can be no doubt that a well-balanced diet is the foremost aim of agricultural policy, it is not true that a well-balanced diet is the foremost aim of agricultural policy.

Intake of total protein is usually sufficient when the calorie yield of the

TABLE XXIII  
Some Indian Diets  
(Ounces per consumption unit\* per day)

Food	1	2	3	4	5	6
	Assam Tea plantation labourers	Madras Berhampore Villagers	Orissa Villagers	Bihar Weirpada admiral family	Central Provinces Villagers	Punjab Villagers
Rice	19.0 (home-pounded and milled parboiled)	21.9 (mostly milled raw)	24.6 (home- pounded parboiled)	21.0 (milled parboiled)	1.5	none
Wheat	none	none	none	none	none	17.4
Millet	none	none	none	none	16.0†	none
Pulses	1.0	0.8	0.9	3.4	2.0	1.9
Leafy vegetables	0.2	0.4	0.3	0.1	none	4.6
Non-leafy vegetables	3.4	2.9	7.7	4.2	4.6	4.6
Fruit	none	0.8	none	0.9	none	2.5
Vegetable oils	0.3	1.2	0.1	1.8	0.3	negligible
Ones	none	negligible	none	(mostly ghee)	none	1.2
Milk and buttermilk	0.5	1.0-2.0	none	5.7	1.8	8.7
Meat, fish and eggs	0.2	0.1	1.1	1.0	0.1	none
Sugar and jaggery	negligible	0.1	none	0.8	negligible	not reported

1 Wilson and Mitra (1938)

2 Nutrition Research Laboratories (unpublished)

3 Narain Singh (1933)

4 Mittal K. (1940)

5 Nutrition Research Laboratories (unpublished)

6 Ahmad and Gore (1933)

\* A consumption unit is the allowance for one male adult; any additional male adult members are counted as one unit, and other members according to the coefficients shown in Table XXIII above.

The populations of which the average diets are shown in the above table are normal populations: none of these surveys was taken in a famine area nor was any particularly poor population of which there are many in India included. In his invaluable *Health Bulletin No. 23* Dr Aykroyd (1941) gives an example of the type of poor and ill-balanced diets that are often encountered in India: this is shown diagrammatically in figure 190 in which a balanced diet suitable for an Indian peasant of a rice-growing district is also shown. An analysis of these two diets is given in the table below.

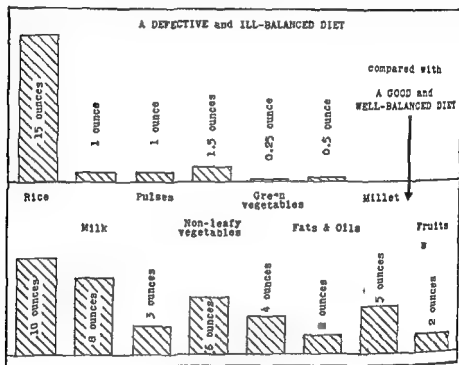
TABLE XXIV

Summary of an ill-balanced and a well-balanced diet

Constituent	Amount in ill-balanced diet	Amount in well-balanced diet
Protein in grammes	38	77
Fat	19	74
Carbohydrate	357	408
Calories	1750	2590
Calcium	0.16	1.02
Phosphorus	0.60	1.47
Iron in milligrammes	9.00	44.00
Vitamin A international units	500	7000
B	160	400
C in milligrammes	15	17

It will be seen that the poor and ill-balanced diet is not only deficient in caloric value, but in almost every item of the protective foods. Three (1, 2 & 5) out of the six average diets in Table XXIII also are below the minimum requirement in calories, and four (1, 2, 3 & 5) are each defective in several important protective elements.

To summarize, it can be said that 30 to 50 per cent of the indigenous inhabitants of India do not eat enough food, and that the diets of the great majority are deficient in several important elements. The diet of the rice-eater is usually deficient in iron, and, under conditions of unusual heat,



chlorides will also be relatively deficient. Many diets are deficient in fat-soluble vitamin A, and in vitamin B-complex unless the people take some form of 'country' beer. Vitamin B<sub>1</sub> is deficient usually only in the diets of the south under

These remarks can probably be applied to the native inhabitants of most other tropical countries, and certainly to those whose staple diet is rice, maize, or some poorer food substance such as tapioca.

**Rice.**—As rice is the staple food of about half the inhabitants of the globe, it is entitled to a few lines of special discussion. There are of course

\* 'Country' beers are crude alcoholic beverages made by fermenting various grains, unlike ordinary beer they are sometimes rich in vitamin B complex.

some scores of not hundreds of varieties of rice plant, but it will not be e The gross nature of meal composition is so that can be applied for

When threshed from the head, the grain consists of an outer inedible husk and an inner edible grain. The latter consists of an endosperm, with its thin outer layer of aleurone cells, the surrounding pericarp, and the 'germ'. The bulk of the endosperm consists of carbohydrate, the aleurone layer contains most of the protein and fat, and the vitamin B<sub>1</sub> is mainly in the germ.

There are several ways of preparing the grain for eating, and the composition of the final product depends largely on the way it is prepared. The primitive method, a method that is still followed by the

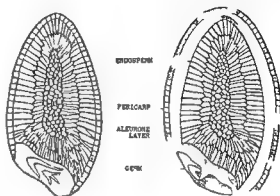


Figure 191: Section of a rice grain showing the effect of milling

large majority of peasants who grow their own rice, is pounding the grain with a heavy wooden pestle in a large wooden or stone mortar. This removes the husk, some of the pericarp, and a small part of the germ. The

loss of protein, fat, iron, and vitamin B<sub>1</sub>. There are different degrees of milling and the extreme degree of milling is carried out by rubbing the rice between two leather surfaces, thus removes the last traces of the aleurone layer and pericarp and leaves a polished pearly-white grain. Rice thus treated

A procedure that has been practised mainly in India and is now spreading to other countries is known as parboiling (part boiling). The rice still in the husk is first soaked in water, then steamed for some time, dried and finally husked by one of the methods mentioned above. Parboiling has the practical advantage that it makes newly-harvested rice more digestible and facilitates husking, but its real value from the nutrition point of view is that both the iron and vitamin B<sub>1</sub>, and to some extent other B vitamins also, in the germ are dissolved and much of these are absorbed by the endosperm, therefore, much less of the iron and vitamins are lost during subsequent husking.

The following table shows the effects of milling and parboiling on the composition of rice

TABLE XXV  
Comparison of Raw Rice and Parboiled Rice

	Raw rice		Parboiled rice	
	Milled	Home pounded	Milled	Home pounded
Protein, per cent	6.9	8.5	6.4	8.5
Fat, "	0.4	0.6	0.4	0.6
Calcium "	0.01	0.01	0.01	0.01
Phosphorus "	0.11	0.17	0.15	0.28
Iron mg "	1.00	2.80	2.20	2.80
B <sub>1</sub> IU per 100 g	20	60	70	90
Digestibility	+++	+	+++	++
Storing properties	good	poor	poor	very poor

There is further considerable loss, up to 50 per cent, of important ingredients during washing and cooking, especially if the cooking water is discarded, which of course it should not be.

It will thus be obvious that the practice of machine milling is a bad one from a nutritional point of view. One might ask 'Why then is it practised and why is it difficult to eradicate the practice?' There are several reasons for this, some of which are sound, others are not. Firstly, (a) the industrial worker finds it very convenient to buy rice ready for cooking instead of pounding it himself. This saving of trouble will often appeal to the villager also and he frequently takes his rice to be milled, this is done almost free of cost, because the miller makes his profit out of the 'polishings'. (b) When rice has to be conveyed some distance, freight would be further, husked

rice keeps well if it is stored in a dry and well-ventilated place, as the husk protects it, but, when the husk is removed, the fat in the aleurone layer is exposed to attack by micro-organisms and becomes rancid very quickly. Parboiled rice, even if subsequently milled, does not keep as well as raw milled rice. Finally, (c) aesthetically a plate of spotless white rice is much more appealing than one of flecked and discoloured, home-pounded rice. Thus, it will be seen that the problem is not altogether a simple one, but the dangers to health in allowing persons who eat little else but rice to use polished rice are so great that it is essential that these difficulties should somehow be overcome.

One method is to limit the degree of milling to which rice may be subjected. Another would be to improve the mechanical methods of husking rice. Experiments have been carried out with a wooden grinder and it has been shown that, by using this, three times as much fat and vitamin B<sub>1</sub> are preserved as when the same sample is subjected to machine milling.

The introduction of legislative measures to prohibit machine-milling is likely to be resisted on account of vested interests. Further, in a locality where the milling has been practised for many years and the people have acquired the habit of buying milled rice in small quantities as they require it, it would be impracticable suddenly to prohibit the milling of rice.

#### THE EFFECTS OF DEFICIENT DIET ON HEALTH

**General Effects.**—It may be taken as axiomatic that the physique of a nation is dependent to a large extent on its food. Numerous examples of peoples of the same racial type living under comparable climatic condi-

tions in which those taking a better diet are physically far superior could

physically much finer types than the rice-eating southern Indian. It is however harder to appraise the effect of diet on health, as distinct from physique, that is, on morbidity and mortality, as so many other factors come into operation. In India, at least a third of the population is quantitatively underfed and an even greater proportion lives on a qualitatively defective diet (*vide supra*), and the health of the country is admittedly

be connected, but how much of this ill-health can be attributed to malnutrition and how much to other factors? The modern sanitarian believes that nutrition is a matter of primary importance. Sir Alexander Russell, then public health commissioner with the government of India, in his report for 1935 wrote —

'No preventive campaign against malaria against tuberculosis or against leprosy no maternity relief or child welfare activities are likely to achieve any

But it is not easy to provide proof from public health returns

Similarly, the clinician cannot fail to believe the importance of diet when he sees the various major and minor defects melting away as his patients are put on to good hospital diet, and their persistence if the same patients are treated in their own homes. But he again finds it difficult to show any proof that these same people would not have suffered the various infections, malaria, amebiasis, kala azar, typhoid, or ancylostomiasis, that probably brought them in to hospital, whatever their diet had been. While there is little indication that the incidence or the course of the disease in the cases of smallpox, plague, kala-azar, sleeping sickness, or yellow fever are affected by the patient's state of nutrition, cholera,

malnutrition, but recently this doctrine has been questioned and some of the leading authorities have suggested that the connection between

except in the ill-nourished. About the association of tuberculosis and malnutrition there is little doubt. The standard example is Germany in the last war, here the incidence rose rapidly, almost certainly as a result of the widespread malnutrition from which the whole population suffered. Finally, though it seems doubtful if malnutrition could determine specific dysentery infections, there are certainly many non-specific 'intestinal fluxes' that are caused by defective dietary (*vide supra*).

Some relevant data can be obtained from famine reports. In India Nicol (1940), reporting on the Hissar famine of 1938 and 1939, showed that there was an increase in mortality of 75 per cent.

stand though one would certainly expect an increase in mortality. The total number of deaths in 1939 was 37,767 as compared with 20,910 in 1937. The increase in the death rate was most marked in the under-ten-years age group, and of the total deaths in 1939, 21,160 were in this age group, that is 56 per cent of all deaths in Hissar were in children under 10 years of age. This is in keeping with the well-established fact that the effects of malnutrition are most noticeable in infants and young children. Forty-nine per cent of all deaths in British India were in children under 10 years of age, if these figures are compared with that for Hissar (56 per cent) and England and Wales (12 per cent), it will be seen that the figure for British India as a whole is much nearer to that of the famine area than to that of England and Wales. The deduction is obvious.

The recorded infantile mortality in British India in 1939 was 155 per 1000 live births, the actual infantile mortality probably being much greater. Another special group in which the death rate is very high is amongst pregnant and parturient women. Maternal mortality has been variously estimated in different large areas in India as from 16 to 25 per mille, and in one investigation in Assam an average figure of 42 was given, with for one group the extraordinary figure of 137 per 1000 births (Balfour 1927), this has to be compared with 282 for England and Wales in 1939. Neal Edwards (1940) found that 23.3 per cent of the maternal deaths in Calcutta were due to anæmia, whereas anæmia was also a contributory cause in many more cases and Napier and Neal Edwards (1941) considered that the main cause of this anæmia was dietetic.

All this points to the fact that malnutrition is an important factor in the production of ill-health and high mortality in India. For other tropical countries, e.g. for Java by de Haas (1939 & 1940), similar figures have been produced, and the writer believes that it is fair to assume that much of the ill health in the tropics is due to malnutrition amongst the native inhabitants.

**Special effects of dietary deficiencies—Starvation.** A person who for any length of time eats less than the amount that may be considered his minimum requirements is being starved. The result of starvation is the loss of body fat, first the adipose tissue of the abdominal wall and the fat in the other parts of the body. Then the muscle followed by the unstriated muscle and eventually the heart. The liver, which is looked upon as a natural reserve, has been used up, the subject becomes lethargic and all muscular effort is reduced to a minimum, after which

there is a slowing down of metabolism, evidenced by a fall of pulse and respiration rate, until a point of compromise is reached, probably in an adult at about one thousand calories daily intake (it will be relatively higher in a child who requires some food for body-building purposes). If the intake falls below this, vital organs will be affected and the subject will eventually die. In complete starvation specific deficiencies do not usually develop, but in partial starvation, these may complicate the picture and hurry the end, scurvy (vitamin-C deficiency) is a common disease during famine.

**Protein deficiency.**—This may be (a) an absolute deficiency as in starvation, (b) a relative deficiency as in pregnant and lactating women and growing children whose protein requirements are relatively far greater than those of adult men, (c) due to the unsuitability of the protein, e.g. zein of maize, or (d) due to the defective powers of assimilation of the individual.

This is the specific deficiency most commonly associated with starvation and oedema which is one of the earliest manifestations is often referred to as 'famine dropsy', the condition is likely to occur when the protein intake falls below 30 grammes daily. There is hypoproteinæmia, the deficiency is mainly in the serum albumin fraction. The oedema is usually confined to the legs, but the whole body may be involved. There is also polyuria and some anæmia but most of the other symptoms that may be associated can probably be attributed to the general starvation. There is of course no ætiological association between famine dropsy or 'war oedema' and it is sometimes called and epidemic dropsy (*vide infra*).

Hypoproteinæmia may occur in late pregnancy and is sometimes associated with anæmia, it occurs in women on a diet which is low in protein and although well above the 30 gramme level, is insufficient to meet the additional demands.

**Vitamin-A deficiency.**—This would appear to be one of the most common defects in tropical diets, partly on account of the low fat intake, and it is surprising that there are not more definite clinical defects attributable to this deficiency. Vitamin A was at one time known as the anti-

ness xerophthalmia, phrynodema and possibly certain types of stone in the kidney. Some of the eye conditions hitherto attributed to vitamin A deficiency have recently been shown to respond better to riboflavin than to vitamin A administration, it seems possible that the action is synergistic and that both should be given.

**Night-blindness.**—The association of night blindness and vitamin-A deficiency is so well established that light adaptation tests with an apparatus known as a biophotometer are employed as one of the standard methods of testing for vitamin-A deficiency. Inability to see at all in a dim light is a common defect in poor populations in the tropics. The condition is often associated with other vitamin-A deficiencies and with anæmia-producing factors. It leads the writer in certain types of



**Xerophthalmia**—This condition of dryness of the conjunctiva is indicated in its earliest stages by the appearance of Bitot's spots white exudates

**Phrynoderma**—Nicholls (1933) in Ceylon Loewenthal (1933) in East Africa and Frazier and Hu (1934) in China reported a follicular hyperkeratosis particularly on the extremities they associated with vitamin A deficiency and named phrynoderma on account of the scaly skin which is a very apt comparison amongst children in several parts of India

**Renal calculi**—McCarrison produced renal calculi in rats by feeding them on a diet deficient in vitamin A and has suggested that the urinary lithiasis that is common in some parts of India might be due to vitamin A deficiency

**Prevention and treatment**—All these conditions can be prevented by increasing the intake of articles rich in vitamin A, these are leafy vegetables (e.g. spinach cabbage celery, amaranth leaves and coriander leaves) carrots fruits (particularly mango and papaya) liver eggs and butter Vegetable oils contain no vitamin A with the exception of red palm oil which contains large amounts of pro vitamin A or carotene which is converted into vitamin A in the body

Medicinal cod liver oil contains very few units (IU)	halibut liver oil as this cod drop contains several thousand units is vitamin A but has to be taken in slightly larger doses a drachm and a half will provide an adequate daily dose of vitamin A
The latter oil, although not so rich in vitamin A contains large amounts of vitamin D and has other nutritional qualities which make it preferable	
During the war the cod liver oil has been difficult to obtain and several substitutes have been tried	shark liver oil has proved valuable
Commercial concentrates are also available	vitamin A probably do not exceed 5000 units
then response may be slow	be the aim in treatment and even

**Vitamin B deficiency**—This vitamin has recently become a popular panacea and is at present grossly abused by the over enthusiastic but it does certainly appear to have a beneficial effect in a large variety of conditions e.g. in the polyneuritis of alcoholism pregnancy and senility and also in certain neuritis of doubtful origin in cardiac failure of obscure origin with hypertrophy in oedema and in anorexia and functional disorders of the intestinal tract due to lack of tone As the diets of rice eating people are very liable to be deficient in this vitamin it is probable that many of the conditions of the nature of those mentioned above from which they may suffer can to some extent be attributed to vitamin B<sub>1</sub> deficiency but the only definite syndrome associated with this deficiency is beri beri this disease will be discussed separately The prevention and treatment of this deficiency will be discussed under BERI BERI

**Vitamin B complex deficiency**—This is a common deficiency in the tropics Many fractions of this vitamin have been identified The quantitative occurrence of each fraction has not been so thoroughly worked out as in the case of other vitamins but as a general rule liver brewer's yeast certain green vegetables pulses meat fish and poultry are the richest

sources Vitamin B<sub>2</sub> complex occurs in large amounts in dried brewers yeast and these are the best medicinal sources. It will be best to consider the effects of these different fractions separately.

**Nicotinic acid or niacin**, deficiency is an important even if not the main factor in the aetiology of pellagra (*vide infra*) it also plays some part in the production of non-specific gastro-intestinal disturbances e.g. sprue (*quod vide*) and toxic psychoses and encephalopathy. As our experience widens it will probably be found that there are many other minor health defects especially skin conditions commonly encountered in the tropics which can be attributed to niacin deficiency.

**Riboflavin**—Evidence of the deficiency of this fraction is much more frequently encountered than that of niacin the main clinical evidence of ariboflavinosis is glossitis cheilosis angular stomatitis and certain eye changes namely congestion of the sclera vascularization and later ulceration of the cornea and blepharospasm associated with photophobia visual fatigue dimness of vision a burning sensation and a feeling of roughness of the eyelids.

There is superficial denudation and redness at the line of closure of the lips maceration fissuring and a yellowish crust formation at the angles of the mouth seborrhoeic dermatitis around the ala nasi and just inside the nose at the canthi of the eyes and on the ears and deep magenta coloration and fissuring of the tongue and swelling and flattening of the papillae or the tongue may show oval or irregular areas of desquamation with atrophic centres and raised pinkish edges. These mouth changes are associated with soreness and burning of the tongue and lips and dysphagia. The subjective eye symptoms often precede the glossitis and angular stomatitis but it may be necessary to ask leading questions to elicit attention. There is immediate response to 5 to 15 milligrammes with definite but it takes several

days to become fully established.

The position of **pyridoxin** (vitamin B<sub>6</sub>) in human metabolism is not yet fully understood but certain nervous symptoms including irritability insomnia and muscular weakness rigidity and painful spasms and cheilosis in pellagra patients myasthenia and muscular dystrophies chilblains and certain forms of anaemia have improved on the administration of pyridoxin in doses of 10 to 50 milligrammes. In rats at least this vitamin appears to play some part in the metabolism of unsaturated fatty acids and it is suggested that its action may be similar in man and that its deficiency is one of the causes of sprue.

There are several other fractions included in the vitamin B complex some of which have been identified e.g. pantothenic acid but the only other common tropical syndrome associated with deficiency of vitamin B complex is **tropical macrocytic anaemia**, the evidence that this is associated with vitamin B<sub>2</sub> deficiency is dependent on epidemiological data and on the therapeutic test that is to say the response to the administration of autolysed yeast extracts (marmite or vegemite) and other substance rich in this vitamin. It has been shown that the isolated vitamins thiamin (B<sub>1</sub>) niacin, riboflavin pantothenic acid and pyridoxin (B<sub>6</sub>) have no effect on this condition.

**Tropical macrocytic anaemia** occurs in men and women living on a poor diet in the latter it is often associated with pregnancy and in both

sexes with chronic malaria. Although there is little doubt that deficiency absolute or relative, of some fraction min-B complex is an important aetiological nutritional deficiencies, e.g. protein or and other factors. The writer has suggested toxicity.

**Vitamin-C deficiency**—Scurvy (*vide infra*) and sub scurvy degrees of vitamin-C deficiency are common in tropical countries particularly amongst labour forces working away from their home surroundings and familiar fruits and vegetables, and during times of famine.

Scurvy is the only definite deficiency in many tropical conditions, e.g. its development is delayed unless sufficient

The prevention and treatment of this deficiency will be discussed under the heading of SCURVY.

**Vitamin-D deficiency**—Despite the fact that many tropical dietaries are deficient in vitamin D, only under very special circumstances does frank rickets occur in the tropics, as the hours of sunshine are many and the majority of people spend much of their time in the open air. However minor degrees of rickets do occur amongst the children of both natives of the orthodox classes who do not allow their children sufficient freedom and of sojourners who are too assiduous in protecting their children from the sun.

There is an adult form of rickets which is common in northern Indian towns in particular, but which also occurs in other countries amongst women who are kept in *purdah* especially when their diet is deficient in calcium. This condition known as osteomalacia is usually first noticed when the woman is pregnant and her calcium is further depleted by the inexorable demands of the foetus. There is softening and bending of the bones particularly those of the pelvis so that parturition becomes difficult or even impossible. The first symptoms are general weakness and girdle pains there may also be tetany. The condition usually becomes worse with each succeeding pregnancy, if the woman survives the earlier pregnancies and no preventive measures are taken.

The first preventive measure is education and the alteration of unhygienic social habits. Otherwise it consists in seeing that all pregnant women get a sufficiency of food rich in vitamin D, calcium and phosphorus and a regular period of exposure to sunlight. Treatment, by appropriate feeding and the giving of vitamin concentrates will only be effective if it is given in the early stages before the bone deformities have become established. Vitamin D occurs in milk and butter (from pasture fed cattle) liver, and fish-liver oil. The last named are the richest source. Cod liver oil or shark-liver oil and the pure vitamin 'calciferol', or some proprietary preparation of irradiated ergosterol (e.g. viosterol) are the forms in which it is usually given.

uns for ex  
the tropics  
portions and

the high neonatal death rate, but the subject has not yet been sufficiently studied to make any discussion on it appropriate here.

The reader should perhaps here be reminded that few deficiencies are single, and when one deficiency condition is known to exist others should be expected and be looked for

#### THE PREVENTION OF NUTRITIONAL DEFICIENCIES IN TROPICAL COUNTRIES

**Causes of malnutrition.**—Before attempting to devise general measures of prevention, it is necessary to enquire what are the causes. There is naturally no single formula that will cover all the causes, even in one country, and there are many countries to consider. As has been suggested above, India may be looked upon as a representative tropical country.

Without going too deeply into root causes, one can say that the principal common cause of malnutrition is poverty. Figures for rural family incomes have been given by various workers, but, as the workers themselves usually claim, these estimates must be taken with considerable reserve on account of the difficulty of applying monetary values, to rural incomes in particular. The average family annual income in Bengal has been estimated as Rs 150/ (250/- £ 111/ 10/- in 1929) that of a poor

just over Rs 4/— In industrial populations, the monthly income per capita is often higher, but this is usually more than counteracted by the higher cost of food and the fact that often little more than half the income is available for food.

The cost of the poor and the balanced diets shown in figure 190 would (in normal times, in most places in rural India) be about Rs 2½ to Rs 3 and Rs 5 to Rs 6, respectively, so that very few of the families in the populations instanced above would be able to afford a balanced diet.

It has been shown in several investigations in India that, with an increase in the income, not only more calories but a greater proportion of protective substances are added to the diet. Thus an improvement in their economic state would not only make it possible for people to purchase a balanced diet, but experience has shown that they will usually do so.

This is of course far from the whole solution to the problem as there are many instances in which through ignorance well-to-do persons live on a diet that though adequate in calories is unbalanced, that is, deficient in protective substances, and still others, in India in particular, in which the income is sufficient for them to purchase a balanced diet but they do not in fact do so because their religious or other prejudices will not allow them to take advantage of all the available sources of protective substances. Further, malabsorption and/or increased metabolism, that are common to many tropical febrile disorders, increase rather than decrease the patient's general and special dietetic requirements, but such patients are usually kept on a low diet, and therefore frequently show evidence of specific deficiencies. This state of affairs which is common in temperate climates (Goldsmith, 1942) is exaggerated in many tropical countries by the local prejudice in favour of starving, not only a fever but any other

TABLE XXVI  
Composition and caloric value of some common foodstuffs

Name of foodstuff	Protein %	Fat %	(Carbohydrate %)	Calcium (C %) <sup>o</sup>	Phosphorus (P) %	Iron (Fe) % <sup>o</sup>	Vitamin A IU per 100 g	Vitamin B <sub>1</sub> IU per 100 g	Vitamin C mg per 100 g	CALORIES PER		Biological value of protein
										100 grammes	ounce	
Rice, raw, home-pounded	8.5	0.6	78.0	0.01	0.17	2.8	4	60	—	351	100	80
Rice, parboiled, home-pounded	8.5	0.6	77.4	0.01	0.28	2.8	15	90	—	349	99	67
Rice, raw, milled	6.9	0.4	79.2	0.01	0.11	1.0	—	20	—	348	99	80
Wheat, whole	11.8	1.5	71.2	0.05	0.32	3.3	108	180	—	346	98	67
Wheat flour, refined	11.0	0.9	74.1	0.02	0.09	1.0	—	40	—	349	99	83
Cholam ( <i>Sorghum vulgare</i> )	10.4	1.9	74.0	0.03	0.23	6.2	136	115	—	355	101	89
Ragi ( <i>Eragrostis coracana</i> )	7.1	1.3	76.3	0.23	0.27	5.4	70	140	—	345	98	60
Maize, tender	4.3	0.5	15.1	0.01	0.10	0.7	42	—	4	341	97	—
Lentil (masoor dal)	25.1	0.7	59.7	0.13	0.25	2.0	450	150	—	346	98	41
Red gram (arhar dal)	22.3	1.7	57.2	0.14	0.26	8.8	220	150	—	333	95	74
Soya bean	43.2	19.5	20.9	0.24	0.69	11.5	710	300	—	432	125	54
Amaranth, tender	4.9	0.5	5.7	0.50	0.10	21.4	2,500-11,000	10	173	47	13	72
Brussels sprouts	4.7	0.5	9.2	0.05	0.08	2.3	210	—	72	60	17	76
Cabbage	1.8	0.1	6.3	0.03	0.05	0.8	2,000	50	124	33	9	—
Celery	6.0	0.6	8.6	0.23	0.14	6.3	0,000	7	62	64	18	—
Lettuce	2.1	0.3	3.0	0.05	0.03	2.4	2,200	100	15	23	7	—
Spinach	1.9	0.9	4.0	0.06	0.01	5.0	3,000	70	48	32	9	—
Carrot	0.9	0.1	10.7	0.08	0.03	1.5	3,000	60	3	47	13	—
Onion, large	1.2	>0.1	11.6	0.18	0.05	0.7	—	40	11	51	14	—
Potato	1.6	0.1	22.9	<0.01	0.03	0.7	—	20	17	99	28	67
Sweet potato	1.2	0.3	31.0	0.02	0.05	0.8	10	—	24	132	37	72
Tapoca	0.7	0.2	38.7	0.05	0.01	0.9	—	—	—	159	45	—
Sago	0.2	0.2	87.1	0.02	0.01	1.3	—	15	—	351	100	—

TABLE XXVI—(Contd.)  
Composition and caloric value of some common foodstuffs

Name of foodstuff	Prote n%	Fat %	Carbohydrate %	Calcium (Ca) <sup>2</sup> %	Phosphorus (P) %	Iron (Fe) mg %	Vitamin A IU per 100 g	Vitamin B IU per 100 g	Vitamin C mg per 100 g	CALORIES PER		Biological value of protein
										100 grammes	ounce	
Cashew nut	21.2	46.9	22.3	0.05	0.45	5.0	100	—	—	596	169	72
Coconut	4.5	41.6	13.0	0.01	0.24	1.7	T	15	—	444	126	58
Ground-nut	26.7	40.1	20.3	0.05	0.39	1.6	63	300	—	549	158	
Apple	0.3	0.1	18.4	0.01	0.02	1.7	T	40	2	56	16	
Banana	1.3	0.2	36.4	>0.01	0.05	0.4	T	50	1	153	43	
Mango ripe	0.6	0.1	11.8	0.01	0.02	0.3	4,800	—	13	50	14	
Orange	0.9	0.3	10.6	0.05	0.02	0.1	320	40	68	49	14	
Papaya ripe	0.5	<0.1	9.5	0.01	0.01	0.4	2,020	—	46	40	11	
Tomato ripe	1.0	0.1	3.9	0.01	0.02	0.1	320	40	32	21	6	
Beef (muscle)	22.6	2.6	—	0.01	0.19	0.8	59	50	2	114	32	98
Pig (fowl)	13.3	13.3	—	0.06	0.22	2.1	2,200	—	—	173	49	94
Milk (cow)	3.3	3.6	4.8	0.12	0.09	0.2	180	17	2	65	18	85
Milk (sterilised)	2.5	0.1	4.6	0.12	0.09	0.2	—	—	1	—	8	
(beef)	24.1	25.1	6.3	0.79	0.52	2.1	—	—	—	348	99	
Red palm oil	—	100.0	39.1	0.44	1.49	43.7	40,000	2,000	—	900	256	
Yeast dried	39.5	0.6	—	—	—	—	110	—	—	320	91	

form of illness a prejudice which is so deeply ingrained in the minds of the people that the medical man even if he is not tainted with the same prejudice will have great difficulty in persuading his patient to take a better diet.

To summarize the principal general causes of malnutrition are therefore poverty and ignorance and as a corollary the first two general measures of prevention will be improvement of economic status and education.

**Measures of prevention**—Improvement of economic status is outside the scope of the medical profession and our duty as ordinary medical men or women in this matter ends when we have demonstrated to the statesman (or the administrator) and the agriculturist the correlation between poverty and malnutrition in any particular country or community though a constant liaison between the agriculturist and nutrition specialist is essential.

But in the matter of education our duty is much wider. Medical education has been backward in the teaching of dietetics and it is first necessary to make up this ground by impressing on the medical man of both today and tomorrow the importance of a sound knowledge of the principles of dietary. This applies more especially in the tropics where the subject is relatively much more important than in temperate climates. (It is on these grounds that the present writer excuses himself for including in the chapter much that all practitioners should and the majority of readers probably do already know.) The next person to be educated is the administrator whether he is a government administrator or the manager of a labour force. Here the advice given must be accurate and based on locally obtained data uncontroversial and practical or it will carry no weight.

Direct education of the population will not be the doctor's work; this must be done through lay health workers and school teachers but it is the business of the medical profession to see that these people understand properly what they have to impart.\* Where there is a public health department this should include a nutrition officer whose duty will include amongst other things education and propaganda.

In addition to these long term nutrition policies it will often be possible to do something more immediate for special groups. The most critical periods when the physiological demands are greatest are during pregnancy and lactation and in childhood. Where maternity and child welfare organizations exist much can be done by advising mothers and giving milk and other protective dietetic substances to both mothers and infants and the school child's home diet can be similarly supplemented during school hours as is done in many western countries. Skimmed milk made from imported powder which is cheap and has a high protein content is worth considering for this purpose also soya bean preparations. When synthetic vitamin preparations become cheaper as they probably will it may be worth ensuring that mothers and children get an adequate supply of all necessary vitamins by giving these to them in pill form and even today it is often worth giving pregnant women iron in the form of ferrous sulphate tablets or a mixture

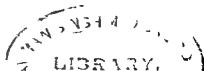
\* From the government of India  
Publications of this kind  
if they are not these two

In the treatment of his own patients the doctor has a special responsibility. He should always ensure that his patient's diet is adequate in all the vitamins remembering that the requirements in the febrile conditions in particular may be above those of a normal person. He should be especially cautious when his patient is subsisting on a milk diet, which is almost devoid of ascorbic acid and iron, and very low in niacin, and when nutrition is maintained largely by intravenous glucose, in which case thiamin will be an additional requirement.

Special problems, such as that of rice, and measures directed against specific deficiencies are discussed under the appropriate deficiency diseases.

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**Definition**—Beriberi is a metabolic disorder characterized by peripheral neuropathy, myocardial weakness and frequently oedema occurring in persons on a diet deficient in vitamin B<sub>1</sub>.

**Historical**—The syndrome known as *lakkle* or leg disease was described in early Chinese literature several hundred years before the Christian era. The name beriberi appeared later and seems to have been derived from a Malayan word *beribi* meaning a jerky gait or from an Indian word *bharbati* meaning a swelling. In Japan it was known by the Chinese name *lakkle* and was described by early writers as occurring in the Dutch East Indies. It was first reported in India in the western hemisphere appeared in 1824 when it was reported in Brazil and

2004

## EPIDEMIOLOGY

**Geographical distribution**—The disease has no geographical limitations. It was for many years looked upon as a purely tropical disease but this was shown by an outbreak in Newfoundland to be a wrong conception and since then isolated cases have been reported in nearly every country in the world. However as at least ninety per cent of cases occur amongst rice eating people the distribution of the disease is mainly tropical. The largest number of cases have been reported from China, Japan (an annual average of 17 000 deaths between 1920-29), Indo China, Siam, Malaya and the Dutch East Indies, the Philippines, India, tropical and South Africa, also Brazil and the West Indies. Small outbreaks have occurred amongst the natives of Western Australia, in Newfoundland and Labrador, in Iceland and in institutions in the United States, Great Britain, France, and Holland.

In India, some confusion has arisen through the popular practice (which is unfortunately sometimes encouraged by medical writers) of referring to epidemic dropsy as beriberi but it is now generally accepted that the only area where the beriberi assumes serious proportions is the north-east coastal area of the Madras Presidency, the Northern Circars (see figure 192).

**Epidemiological status**—It is not a truly epidemic disease (see p. 324) but the appearance of outbreaks that involve a large number of persons living in close contact and of course always on the same diet, give the semblance of an epidemic. Nor as far as is known is it in any way dependent on local conditions except in so far as these affect the food supply of the population. As noted above it occurs mainly in native populations whose staple food is milled rice. It has also appeared in armies, labour forces and amongst the inmates of institutions similarly fed, and has disappeared when the diet has been changed to uncrushed rice, or some suitable supplement has been added. Outbreaks not associated with milled rice have been reported amongst people who have lived for some

time on a monotonous diet with white flour as the staple substance e.g. in Newfoundland, where the diet was almost solely white bread and molasses for certain months of the year, and in institutions, usually mental asylums where white bread was used. It has also occurred on ships where



Figure 192 Map showing distribution of beriberi in southern India in 1938 and the number of cases of beriberi treated in each district during that year (Åkroyd et al., 1940)

ships biscuits made from white flour and tinned foods have been the principal diet

It is a disease of towns rather than rural areas

**Seasonal incidence**—In most places where the disease occurs there is some season during which it is most prevalent, but this is not by any

means the same season in different places. Much capital has been made out of this seasonal incidence by the champions of different theories who can usually find from the varied data some that suit their particular theory. For example in the Godavari delta (Southern India) the incidence of beriberi is high in September and low in January, this no doubt would be attributed to the stored rice becoming damp during the monsoon, by the supporters of the rice infection or rice toxin theories but Aykroyd and Krishnan (1941) find quite a different explanation namely that when the rice is freshly harvested at the end of the year it is not suitable for consumption unless it is first parboiled so that in this district 56 per cent of the rice eaten in January is parboiled whereas in September the last year's crop is mature and can be eaten without previous parboiling, and only six per cent of rice eaten in this month is parboiled\*. In nearly every case the seasonal incidence can be similarly explained in terms of the present theory of the aetiology of the disease (*vide infra*)

**Age, sex, and race incidence**—In a mixed population the disease is undoubtedly less common in children than in adults though it does occur amongst the former. There is also a form of infantile beriberi that occurs in the breast fed infants of mothers with beriberi. More men than women are affected, but there is little evidence of any true sex preference except that possibly in the working labourer the caloric requirements are greater he will eat more rice, his vitamin B<sub>1</sub> requirements will be correspondingly greater and he is therefore more likely to show evidence of the deficiency. The more probable explanation is however that there are usually more men than women in the type of population that is affected.

There is little evidence that any one racial type is more susceptible than any other, the fact that European personnel of institutions escape the disease when native soldiers or native inmates suffer can of course be explained on the differences in their dietary.

### ÆTIOLOGY

**Historical**—The story of the discovery of the cause of beriberi forms an important part of the story of the discovery of the vitamins.

The first worker to recognize the dietetic nature of beriberi was Takaki. In 1884 he recognized the dietetic nature of beriberi in the personnel of the mixed diet which had been established for the personnel of the

In 1890 and the two succeeding years Professor Eijkman working in a laboratory in Batavia that had been established for the study of beriberi produced 'polyneuritis' in fowls by feeding them on polished rice and cured it by giving ground rice. He did not suggest that the disease was the inference was obvious. Professor Eijkman carried the work further and came to the conclusion that the absence of some essential ingredient in the polished rice was the cause of the disease. The work of these two workers on beriberi and in government institutions in Java.

In 1907 the Kuala Lumpur those that a that a part significance is

In 1909 Fraser and Stanton carried out some planned feeding experiments with Japanese labourers they confirmed the above observations but also showed by interchanging the experimental groups that locality had no influence on the devel-

\* Parboiling saves the vitamin B<sub>1</sub> see p 757

opment of the disease and that it was not transmissible from one man to another. They also carried out experiments with fowls that showed in addition to the facts already elicited by previous workers that storage in a damp place had no detrimental influence on rice *versus* beriberi but that if the whole rice grain was subjected to autoclaving at 130°C for an hour it would produce polyneuritis in birds in exactly the same way as polished rice, this experiment incidentally also showed that no living infective agent in the rice was responsible for the disease. Other confirmatory experiments were carried out by Strong and Crowell (1912) and by Vedder. Casimir Funk, working at the *Lister Institute* isolated a protine the word *vitamine* alkaline vitamin B was introduced by Williams.

Many other theories were advanced regarding the nature of beriberi. Several so-called causal organisms were isolated and the theory that badly stored rice developed some special toxin was strongly supported although this last theory

**The present position**—It is generally accepted today that the essential aetiological factor in the syndrome beriberi is a deficiency, absolute or relative, of vitamin B<sub>1</sub>, the pure form of which is known as thiamin or aneurin. Whenever the disease has occurred in a community, it has been possible to show that the staple food was milled rice or some other cereal which in its preparation has been deprived of the bulk of its natural vitamin B<sub>1</sub>, alteration of the diet so that it includes an adequate amount of this vitamin has always led to the disappearance of the disease from that community, and administration of large doses of the vitamin will always cause a disappearance or at least marked improvement in the specific symptoms of individual sufferers.

In a community in which there is a low intake of vitamin the individuals most likely to suffer from beriberi will be those who take an exceptionally large amount of carbohydrate, pregnant and lactating women, hyperthyroid individuals and subjects with febrile diseases, all of whose normal requirements of vitamin B<sub>1</sub> are increased.

Sporadic instances of beriberi, if they cannot be explained on the grounds of actual deficiency of vitamin B<sub>1</sub> in the food taken as in the case of long continued dietary restriction or of chronic alcoholism when the appetite is dulled and alcohol itself acting as a pure carbohydrate provides a large proportion of the calories, can be traced to malabsorption <sup>of the</sup> <sup>vitamin</sup> <sup>these</sup>.

Thus to summarize, the causes of this disease are (a) absolute deficiency of vitamin B<sub>1</sub> in the diet, (b) a deficiency relative to the special requirements of the individual (c) failure of absorption of vitamin B<sub>1</sub> and (d) failure of storage and utilization.

It is frequently claimed, especially by workers who still have a leaning towards some of the earlier discarded theories, that the deficiency of vitamin B<sub>1</sub> is not the whole story of the aetiology of beriberi. This is of course very probable, one might almost say quite certain as what single aetiological factor is the whole story of any disease? In an infectious disease there is always the seed and the soil to be considered, similarly in

an induced metabolic dysfunction both the patient's previous metabolic state and superimposed infections may well help to determine morbidity. Further it is probable that if one vitamin is deficient others will also be deficient and these other deficiencies may contribute to the clinical picture. And having decided that it is purely an avitaminosis, do we know how a deficiency produces a disease and can we entirely discard the possibility of other factors?

**Vitamin B requirements**—The figure usually given is 330 to 660 international (IU) or 1 to 2 milligrammes. The higher figure will include such special classes as pregnant and lactating women. However it has recently been shown that the vitamin B requirements vary according to the carbohydrate intake and it is now usual to express the vitamin B<sub>1</sub> requirements in terms of the calorie intake; it is suggested that the lowest safe amount is 0.25 IU per calorie (Williams and Spiess 1938) which in the average man will be above the maximum indicated above. However when most of the calories are from carbohydrates this figure will not be too high. Fat spares vitamin B and when the latter is deficient the body fat is drawn upon to reduce carbohydrate metabolism to a minimum when this vitamin is exhausted carbohydrate metabolism increases and symptoms of diet deficiency appear. In the case of beriberi, the diet is usually deficient in all the vitamins, and the symptoms are those of a general vitamin deficiency.

day.

The work of Mills (1941) with rats suggests that tropical conditions may increase the requirements of vitamin B. This is interesting in view of the fact that beriberi is more common in tropical countries but it should be confirmed with other animal species and by human experiments in view of the contradictory fact that tropical heat reduces basal metabolism.

**Sources of vitamin B**—The best sources of this vitamin are pork, whole grain cereals and their products, beans and peas, yeast and liver. Although milk, meat other than pork, and fruit do not contain much vitamin B<sub>1</sub>, it is present in small quantities in most natural foodstuffs. It is however often discarded or destroyed in the preparation of these for consumption e.g. in the milling of rice and other cereals in cooking and in canning. It is destroyed by heating to 130° C in one hour; it however, withstands boiling in an acid medium but is destroyed in an alkaline medium.

Recent work (Najjar and Holt 1943) suggests that in certain circumstances thiamin may be synthesized in the human intestinal canal. The implications of this observation are very great and although it is not clear what determines the synthesis it seems likely that the nature of the staple diet or of other non vitamin dietary factors may have some influence.

For further details regarding the source of this vitamin the reader is referred to the tables and discussion on rice in the previous chapter.

#### PATHOLOGY

**Morbid anatomy**—The whole body is wasted and all subcutaneous fat has disappeared; this may be masked by oedema. There may be gen-

eralized oedema with fluid in the serous cavities. This oedema is not necessarily due to cardiac failure as it often occurs in a person with a competent heart but to a breakdown in the mechanism that controls the interchange of fluids and maintains the water balance of the tissues it is more marked in the more acute cases. The changes in the peripheral nerves are degenerative neuritis in inappropriate the sciatics and their branches rarely the cranial nerves. Their extent according to the severity and duration of the affection there may be barely de sheath only with of some of the ax whole nerve.

As well as the peripheral nerves scattered fibres in the tracts cells of the anterior and posterior horns and the sympathetic ganglia are affected. There is heart failure and death.)

Microscopically the most striking feature is intercellular oedema. There is also fragmentary necrosis of the cells its effect on the cells but it is possible that both factors operate.)

**Biochemistry**—Vitamin B is absorbed in both the small and the large intestine. It is stored in the liver and kidneys but it is also found in other organs and tissues. It is excreted in the urine and the amount excreted is a good indication of the vitamin B<sub>1</sub> state of the organism. In health the average daily excretion in an adult is 20 to 30 IU being higher in men and this may fall as low as 3.5 IU in beriberi. The vitamin B<sub>1</sub> + 2 γ or about 2 to 4 IU per good indication of saturation goes to show that vitamin B<sub>1</sub> carbohydrate and controls it is certain that the vitamin B requirements vary according to the carbohydrate intake. It is suggested that this intermediate product is (at least in the case of some carbohydrates e.g. rice) of a toxic nature.

It has been found that the pyruvic acid in the blood and body tissues varies inversely with the vitamin B intake. The normal level of pyruvic acid in the blood is 0.5 to 1.0 mg per 100 grammes. It rises considerably in acute cases of beriberi but is restored to normal by vitamin B<sub>1</sub> administration. In more chronic cases it may be demonstrably increased. A sharp and prolonged rise in the blood pyruvic acid after intravenous glucose constitutes a useful test for vitamin B deficiency.

**The urine**—This will not show any characteristic changes. It will be scanty and there may be anuria during the severe cardiac attack. On resumption of the flow there will be a heavy cloud of albumin and granular casts. The vitamin B content has been discussed above.

**The blood picture**—There is often a marked macrocytic anaemia. Although this may be due to associated deficiencies the writer has seen cases

in which the anaemia appeared to respond specifically to thiamin chloride injections. The lymphocytes are reduced and in the infantile form small lymphocytes may be absent.

### SYMPTOMATOLOGY

**Introduction**—The beriberi syndrome is a clear cut one, quite distinct from any other recognised syndrome but nevertheless as in almost any disease there are distinct clinical types the distinction being due to the predominance of different symptoms which in turn are dependent to some extent on the type of dysfunction. In most outbreaks one type will predominate and this fact has led Vedder to be un B either of which may be possible explanation it is not

entirely necessary in order to classify the

are (a) the acute fulminant

or wet form and (c)

The acute fulminating form

from the wet form he may pass into the chronic form. There will of course be obvious cases of beriberi that will defy accurate classification.

It is usually about three months after the diet has become deficient in vitamin B<sub>1</sub> that the first symptoms appear if the deficiency has been very complete the time may be shorter.

**The fulminating form**—After perhaps a few days of prodromal symptoms such as anorexia, gastro-intestinal disturbances, easy fatigability or in some cases without any warning the patient becomes breathless and cyanosed. He complains of severe epigastric or sub-sternal pain and often vomits. He may also suffer from aphonia (the result of pressure by the right auricle on the recurrent laryngeal nerve). His heart is greatly dilated, the veins in the neck stand out and the liver becomes large, tender and pulsating. The systolic blood pressure is usually lowered and the diastolic very low indeed. The patient dies suddenly within a day or so of the first onset of symptoms with acute circulatory collapse.

**The oedematous form**—In this form the onset is a little more gradual after a short but definite period of ill health. Often with gastro-intestinal symptoms there is a gradual onset of oedema with tiredness and shortness of breath on exertion. The oedema at first only in the extremities gradually extends until it involves the trunk. Eventually there is general anasarca. There are usually some symptoms of peripheral neuropathy but as the other symptoms confine the patient to his bed they are easily overlooked. Wasting is masked by the oedema.

The heart is usually dilated, the apex beat is diffuse and fluttering, the pulse is soft and rapid, the veins in the neck are prominent, the liver is enlarged and tender and the pleural cavities fill with fluid but usually the lungs remain clear until a terminal oedema develops. The blood pressure falls as in the acute form with the relaxation of the peripheral tension. An injection of adrenalin further lowers the diastolic blood pressure almost to zero but pitressin causes a rise in blood pressure that is maintained for an hour or so. The electrocardiogram may show right axis deviation and flattening of the T waves, also prolongation of the Q-T interval and a low QRS complex.

**The chronic, polyneuropathic form**—The onset of this type is far more gradual and for some weeks the patient may struggle on with his



work complaining of loss of weight, weakness, slight breathlessness on exertion headache and vague pains, stiffness and lameness of the legs. The only objective symptom may be tachycardia. The condition increases and he becomes less able to carry on his work. He now complains of numbness and a burning sensation of the feet as well as stiffness of the legs and he finds difficulty in rising from a sitting posture, the calf muscles are tender on pressure and areas of hyperæsthesia appear which later become anæsthetic, knee jerks which were at first slightly exaggerated now disappear and so do the ankle jerks. The definite characteristic ataxic high-stepping gait appears. The condition then spreads to the upper limbs, there is wrist drop, wasting of the hands and fore arms and inco-ordination of the movements of the hand so that the patient drops things easily and is unable to pick up small objects. Chvostek's sign (fibrillary tremors of the muscles on being tapped) may be present.

The muscles of the limbs become wasted and show the typical reaction of degeneration. The patient gradually becomes emaciated, helpless and bed-ridden. The sphincters are usually normal. The condition remains clear. There is usually no increase of cardiac symptoms, otherwise the patient remains good but he may die of hypostatic pneumonia or some other complication.

Irreversible changes take place in the nerves, contractures occur in limbs and even if he lives the patient becomes irreparably crippled.

**Sporadic or conditioned beriberi** \*—The beriberi that occurs in well fed population in special individuals e.g. pregnant women alcoholics etc (*vide supra*), usually takes the chronic peripheral neuropathy form but with recognisable cardiac signs and symptoms, and quite often a variety of other symptoms suggestive of neurasthenia. However, acute cardiac attacks have been reported.

**Sub-clinical beriberi**—Positive evidence of a fact already assumed by many workers, namely that in a population in which there are many cases of beriberi there will be many other persons on the threshold of clinical avitaminosis, is rapidly accumulating, now that biochemical tests for this vitamin are within the scope of the medical investigator—even if not of the ordinary practising physician and there are several relatively simple clinical tests (*vide infra*). Although these minor degrees of B<sub>1</sub> avitaminosis may be classed as sub-clinical, if the person is examined and questioned carefully, some of the minor signs and symptoms e.g. tachycardia, breathlessness on exertion anorexia stiffness and vague pains emotional instability and mental depression may be elicited.

#### DIAGNOSIS

This can be considered under a number of headings—

- (a) The patient's environment diet and habits
- (b) The clinical picture

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\* The writer has avoided the word *secondary* because he considers it misleading and believes that eventually it will be dropped. It is extremely probable that in any outbreak of beriberi in a population living on a diet deficient in vitamin B<sub>1</sub>, morbidity is determined by some secondary factor in nearly every case whether it be slight hyperthyroidism a febrile infection e.g. malaria or the consumption of a larger amount of rice than the rest of the population. It would be unreasonable to consider such cases *primary* whilst labelling as *secondary* a case of beriberi associated with pregnancy.

- (c) Clinical tests including the therapeutic test  
 (d) Biochemical tests

Little further need be said about (a) and (b). It is unlikely that an outbreak of oedema or neuritis in a poorly fed population would fail to arouse one's suspicion but sporadic cases very often will in fact, there is evidence that until a few years ago the majority of such cases were wrongly diagnosed. The conditions for which they may be mistaken are considered below.

(c) Of the clinical tests, the most valuable is the therapeutic test but it is very liable to be misleading in that in so many conditions a B-avitaminosis may be superimposed on some other condition so that immediate improvement on administration of thiamin chloride does not provide the whole answer conversely where there are other deficiencies besides that of vitamin B the slowness of the improvement after the administration of the pure vitamin does not altogether exclude beriberi. However a few doses (ten may be considered the maximum) or even a single dose of 10 milligrammes given intravenously will often produce dramatic improvement in the leading symptoms. This applies especially to the cardiac condition in the polyneuropathic form the improvement will be slower and in advanced cases of nerve degeneration there will be none.

Other tests for vitamin B saturation have been suggested. In a case of deficiency adrenalin will cause a further sharp fall often to zero in the already low diastolic blood pressure or as a variation the rise—if rise there is—in systolic blood pressure after the administration of adrenalin will be greater if a large dose of thiamin chloride has been given previously. Another test is associated with the diuretic effect of thiamin in the deficient individual this is considerable. Finally the circulation time which is usually prolonged in cardiac failure is normal or decreased in beriberi.

(d) Of the biochemical tests, the best indication is obtained from the excretion of vitamin B in the urine the average daily excretion in a normal person is from 20 to 30 IU and in a patient with beriberi about 3.5 IU. After the urine within the figure is much but it is probable that easier and more satisfactory tests will be devised.

**Differential Diagnosis**—The neuropathies have to be distinguished from those of arsenic lead triorthocresyl phosphate (lake) and other poisons from diphtheritic paralysis from rheumatism and various myo-

The oedema has to be distinguished from that of kidney and organic heart disease and which the

In most of these conditions if the case is a typical one there are one or more characteristic signs or symptoms that will differentiate them sharply from beriberi enumeration of these does not seem to be called for here.

## PREVENTION

This can of course be summed up in the single sentence 'increase the intake of food rich in vitamin B<sub>1</sub>'. There is however more to be said on the matter than this. Let us first take the sporadic case: this usually presents little difficulty. In conditions such as pregnancy, hyperthyroidism it is advisable to recommend the regular taking of extract of yeast or neopolishings or some medicinal form of vitamin B<sub>1</sub>, as well as food rich in this vitamin (*vide supra*). This also applies to patients put on to a restricted dietary for any reason. In gastritis or pernicious vomiting it is advisable to give the prophylactic thiamin chloride parenterally.

The real problem is the prevention of beriberi in large and poor populations. The problem is discussed in

with this disease. As was noted above, it occurs amongst rice eating people. The whole edible portion of the rice grain contains quite sufficient vitamin B<sub>1</sub> to ensure the proper metabolism of the whole grain but when the grain is milled in the raw state much of the vitamin is lost and when it is washed and cooked and the water discarded more of the already depleted vitamin is wasted. Parboiling prior to husking saves most of the vitamin. If therefore people will first parboil their rice, home pound it instead of allowing it to be over-milled, clean it—if this is necessary—in the dry state, cook it with the minimum of water and utilize the rice water in their food, beriberi will not occur. In populations where milling has been established for some time there are many practical difficulties in instituting this ideal procedure which are dealt with on p. 758 where also a common-sense procedure of limiting the degree of milling is discussed.

The same problem has to be faced in the case of other cereals: the case of white flour, which is also deficient in vitamin B<sub>1</sub>, but which for aesthetic and other reasons is often preferred, has been met in some countries by 'fortifying' the white loaf by the addition of synthetic thiamin chloride.

## TREATMENT

The treatment can be considered under three headings: specific, dietetic, and symptomatic. It may be argued that the specific and the dietetic treatment cannot strictly speaking be separated but, as in many cases it will be advisable to give thiamin chloride in addition to any special diet, a chemical and dramatic consideration of it as

**Specific.**—It will naturally not be possible to give thiamin chloride to every member of a large community in which the majority of the people are suffering from either frank or sub-clinical beriberi, nor is a large percentage of the cases of all frank cases of beriberi as possible for one can seldom be cured. It has been shown that the best results are obtained when generous doses are given and for an adult a daily dose of at least 20 mg. should be given either intramuscularly or intravenously for ten days to a fortnight after which the dose can be reduced considerably or thiamin (10 mg.) dried

Brewer's yeast (6 ounces) or marmite (or vegex) (2 ounce) can be given by mouth. Infants can be given 3 mg of thiamin chloride daily with safety in fact it is very doubtful if there is any limit to the dosage. In acute cardiac cases doses of over 100 mg have been recommended but the writer believes that 25 mg is about the maximum effective dose. The development of sensitivity to thiamin chloride has been reported so that there may be danger in intermittent parenteral treatment. The dose should be not spaced too widely and if treatment has to be restarted after an interval a small test dose should be given first. There is much to be said for combining the parenteral thiamin with yeast extract as the latter contains other vitamins particularly those of the vitamin B complex group that are probably also in deficit.

**Dietetic**—Rice should be excluded from the diet at first because of its high carbohydrate content but also because of the possibility that intermediate products of metabolism of the rice carbohydrates may be especially toxic. The patient should be put on a diet composed of substances low in carbohydrate and high in vitamin B content such as egg yolk, liver, pork, oatmeal, peas, beans, cauliflower, parsnips, radishes, nut, and soya beans. Later milk, whole meal bread or other whole grain cereal and any substance other than rice that he normally includes in his diet may be added or substituted and eventually he may be allowed to return to his rice diet but it must be undermilled and parboiled and the addition of vitamin B<sub>1</sub> containing substances should be recommended.

**Symptomatic**—In the severe cardiac case the patient must be confined to bed, put on a light solid diet with the fluid intake reduced to a minimum. Præcordial pain is necessary to let a little this should be avoided if be embarrassing the heart should be removed. A saline purgative should be given. Intravenous thiamin in large doses as recommended above will usually produce diuresis reduce the oedema and relieve the heart but if anuria continues one resorted to Digiprophanthus has Oxygen given

Little can be done to relieve the neuropathy beyond the specific and dietetic treatment but massage and electric treatment will help to maintain the tone of the muscles until the nerves recover. It may be advisable to use splints to prevent wrist and foot drop.

#### PROGNOSIS

In fulminant cases either adult or infants the prospect is usually hopeless in any case in which there are cardiac symptoms it is bad but immediate and efficient treatment may save the patient and in the severe neuropathic cases permanent disability may result but in the earlier cases when only a few nerve fibres have degenerated suitable treatment will lead to complete recovery.

In the acute cardiac attack in sporadic beriberi where there is no background of long continued vitamin B<sub>1</sub> starvation, there is often a dramatic response to large parenteral doses of thiamin.

## INFANTILE BERIBERI

Most of the evidence suggests that this disease is the same as adult beriberi but there are special epidemiological and clinical features that make it more convenient to discuss the infantile form separately.

### EPIDEMIOLOGY

It occurs in the infants in a population living on a diet low in vitamin B<sub>1</sub> content and usually in one in which there are numerous cases of adult beriberi. The highest incidence is in the second to the fourth months of life in infants that are entirely breast fed but it also occurs in infants that are partly breast fed or even not breast fed. The mothers are usually found to be suffering from minor degrees of chronic beriberi but they may show no clinical evidence of beriberi at all. It is believed that the particularly high infantile mortality in countries subject to beriberi can be attributed to the high incidence of infantile beriberi. This has recently been emphasized by Aykroyd and Krishnan (1941a) who have carried out a survey in the Northern Circars district of Madras one of the worst beriberi areas in southern India and have shown that the peak of the infantile death rate curve in this and other beriberi districts is not as usual at the first month, but at the second to the sixth month.

### ÆTIOLOGY

There are two schools of thought on the ætiology of the disease both point out that in order to allow for the low intake of vitamin B<sub>1</sub> in the first few months of life the fetus must store the vitamin as it does iron but in this case unlike that of iron where the infant draws almost the last milligramme from its mother both mother and child share the deficiency. The adherents of one school however believe that the beriberic mother secretes some toxic intermediate incompletely oxidized product of carbohydrate metabolism which is neutralized by the infant's stored vitamin B<sub>1</sub> until the latter is exhausted while the adherents of the other school e.g. Vedder believe that the already low vitamin B<sub>1</sub> level of the infant of a beriberic mother is lowered still further to the clinical threshold by the particularly low vitamin B<sub>1</sub> content of the beriberic mother's milk (Sundararajan (1941) has shown that the vitamin B content of the milk of beriberic mothers is not consistently low but in any case the vitamin B calorie coefficient of human milk is much below the necessary 0.25 IU).

**Clinical picture**—Several classifications have been suggested but for practical purposes the cases can be divided into acute and chronic. The acute form usually occurs in breast fed infants within the first three months of life after a short period of anorexia and restlessness or in some cases without any previous warning the infant has convulsions vomits becomes cyanosed and dyspnoeic cries out with acute pain if it is not aphonic, and dies of acute heart failure within as short a time as a few hours in fulminating cases. In the chronic form there are gastro-intestinal disturbances wasting aphonia and dysphagia and generalized oedema. The chronic form may terminate suddenly with a fulminating attack and more rarely an acute attack subsides and becomes chronic.

### PREVENTION AND TREATMENT

Preventive measures applied to the whole population will naturally prevent this disease in infants but any special measures must be applied

to the mother as well as to the child. In beriberi districts the diet of even apparently healthy mothers should be supplemented by B<sub>1</sub> concentrate.

The first step in treatment is to take the infant off breast feeding and to give it a diet rich in vitamin B<sub>1</sub>, but it will also be necessary to add concentrates either recognised commercial concentrates, or some more homely substance such as *tiki-tiki*, which is an extract of rice polishings made by absorbing vitamin B<sub>1</sub> on acid clay. In acute cases the parenteral administration of thiamin in 1000 IU doses is recommended.

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**Definition**—Pellagra (*pelle* = skin *agro* = rough) is a non infectious disease occurring in epidemic like outbreaks mainly in poor populations whose staple diet is maize and also sporadically in other population groups. It is associated with a deficiency of vitamin B complex especially of niacin in the diet and it is characterized by gastro intestinal disturbances dermatitis mental deterioration and eventually if the disease is uncontrolled death. (The mnemonic five Ds—namely Deficiency Diarrhoea Dermatitis Dementia Death—is applied to it)

country after another according to early medical historians who of course may have been prejudiced by their inclination towards the maize theory of the origin of pellagra. In 1776 pellagra assumed serious proportions in Italy and legislative action was taken to control the sale of maize on this account.

A century later the disease during the years 1900-1910 caused a high death rate per 1000 population in some countries.

## EPIDEMIOLOGY

**Geographical distribution**—The disease has a wide distribution in the temperate sub tropical and tropical zones it is a disease of poor and backward countries rather than of hot ones. The association of the disease with maize as a staple diet is responsible for its higher incidence in subtropical countries.



Figure 193 Patient suffering from *mal de la Rosa* (pellagra). From Casals *Memorias de Historia Natural de Asturias* (1762)

As well as those European countries already mentioned other Southern European countries have suffered considerably from the disease. In 1918 it was estimated that there were 70 000 cases in Roumania and further east in Transcaucasia three to four per cent of the whole population were affected and in France Germany Denmark and other northern European countries it occurs sporadically. In Africa, it is not uncommon in the Mediterranean countries from Morocco to Egypt in the Sudan and Abyssinia and amongst the Kaffirs and Zulus in central and southern Africa. In Asia, it has been reported from Syria and Asia Minor China the East Indies and the Philippines and Japan. In India, Lowe (1931) drew attention to it at a leper asylum and since this date sporadic cases and small outbreaks have been reported from many parts of India. In Calcutta we have diagnosed about a dozen cases a year all sporadic for several years past.

In the Western Hemisphere, it was estimated that in 1916 there were 150 000 pellagrins of whom about 10 per cent died. It is still endemic throughout most of the southern United States today. Isolated cases have





# **ETIOLOGY**

**Historical**—The earliest theorists associated pellagra with maize but as all

In 1913 Goldberger and his coworkers in the United States demonstrated that the disease could be eliminated by giving diets with a higher protein content and for a time he considered that it might be due to the general protein deficiency of a maize diet or to a deficiency of some specific amino acid that did not occur in the proteins of maize. Later however when he found that it could also be prevented by a yeast preparation that was practically protein free and had been heated to destroy the heat labile vitamin B<sub>1</sub> fraction he revised his earlier opinion. Eventually the pellagra preventing (PP) fraction of vitamin B was further broken down into riboflavin, nicotinic acid afterwards called niacin etc (see p 763) and Elvehjem demonstrated that niacin would cure pellagra. It has been confirmed by many workers that in most cases the administration of niacin will effect a complete cure of pellagra in a very short time. Niacin was first synthesized in 1879 and was isolated from rice polishings by Funk in 1911 but discarded by him because it did not cure beriberi.

This is not however the end of the story of the etiology of pellagra which many people still believe to be an unsolved problem. Before discussing the position as it stands today it will be as well to review the various theories that have been put forward.

(1) **The maize infection theory**—It has been suggested that in cer

... experimental support for this theory

(2) **The maize toxin theory**—The neurological changes that occur appear to be of toxic rather than bacterial origin and support has recently been given to this theory by the occurrence of pellagra amongst individuals taking maize alcohol but there is no evidence experimental or otherwise to indicate the actual nature of this toxin and attempts to isolate it have failed. Further many people have taken maize as their staple diet all their lives and have never suffered from pellagra and yet others who have never taken maize suffer from it.

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toms run par  
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rays as ergosterol is converted into vitamin D but here again support for this theory is lacking.

(3) **Protein deficiency**—This theory is dependent on the fact that all pellagra producing diets are low in protein content. Maize has a low

protein content compared with other cereals, and, further, the biological value of the protein is also very low. The two facts combined make maize a very poor source of good protein.

(iv) **Specific protein or amino-acid deficiency**—Maize is defective in protein not only quantitatively but qualitatively, and there are for example certain important amino-acids absent from maize protein or *e.g.* tryptophane and lysine. It was suggested that some such specific deficiency is the cause of pellagra.

(v) **Vitamin deficiency** **absence of the PP factor from the diet**—The PP (pellagra-preventing) factor is part of the vitamin B complex which contains amongst other vitamins, niacin, lactoflavin or riboflavin and pyridoxin (B<sub>6</sub> or anti-dermatitis (rat) factor). Food that is rich in vitamin B<sub>2</sub> such as yeast, meat, and liver extract, rapidly cure uncomplicated pellagra, even in patients who are left on their otherwise pellagra producing diet. More recent work, referred to above, has identified niacin as the specific PP fraction, and the synthesized vitamin will control many of the specific symptoms of the syndrome.

For this theory support has been obtained from animal experiments. Dogs fed on pellagra-producing diet develop a condition known as 'black tongue' this condition clears up rapidly when vitamin B complex is added to the diet and is considered to be analogous to pellagra in man. It has been found that the B complex that is specific for the dermatitis produced in dogs is the vitamin B<sub>2</sub> complex which, though it has been named 'rat pellagra', is apparently not analogous to the human disease does not respond to niacin, but improves when vitamin B<sub>2</sub> is given.

**The present position**—This can best be stated by first enumerating some of the established facts.

(a) Niacin in suitable doses will effect a complete and dramatic cure in most cases of pellagra but of course the condition is likely to return unless the patient changes his diet.

(b) In other cases, niacin cures his skin lesions but we require for their cure the riboflavin for the cheilosis neuropathy.

and

(c) In yet other cases of apparently typical\* pellagra niacin has no beneficial effect at all some of these patients respond to liver extract but others are totally refractory.

(d) Analysis of foods for their niacin content has brought to light many anomalies. *e.g.* Aykroyd and Swaminathan (1940) have shown that the rice diet taken by many millions of people in India is a much poorer source of niacin than the maize diet of certain pellagrins. However, some workers question whether at present chemical methods of estimating niacin in foodstuffs are sufficiently accurate to base any important conclusions on such estimations.

\*Some workers deny the fact that the true pellagra syndrome ever fails to respond to niacin given both orally and parenterally.

are required

The complete explanation of (c) does not seem possible on known facts and necessitates introducing a more hypothetical explanation. It has been suggested that there is an intrinsic and an extrinsic factor the latter being niacin and the former not, of course the same as the intrinsic factor deficient in pernicious anaemia but closely related to it, for all pellagrins shows achlorhydria or hypochlorhydria. There is certainly evidence that the individual make up of the patient *e.g.* his endocrine balance determines to some extent the onset of pellagra in one person and not in another on a similar diet and probably also the response to treatment. Cases have been reported which suggested the existence of antagonistic action between thiamin and the PP factor (Lehmann & Nielsen 1939). The writer has recently reported a case (Napier & Chaudhuri 1943) in which pellagra was apparently controlled by means of thyroid extract. Is it possible that the antagonism lies in the fact that beriberi is associated with hyperthyroidism and pellagra with hypothyroidism?

Observation (d) is puzzling. It seems to the writer that no explanation of the aetiology of pellagra can be accepted that does not take into consideration the past and present predominance of the disease amongst people whose staple food is  $\pi$  which by itself  $\equiv$  not  $\pi$  with the vitamin amount of niacin is  $\epsilon$  when this is present in a diet the normal requirements of niacin are increased. As alternatives to the theory of a toxin produced by the effects of external agents *e.g.* bacteria on the maize grain it is possible that some intermediate product of metabolism of maize protein or maize carbohydrate  $\equiv$  toxic or at least capable of fixing the niacin or to carry theoretical considerations further that niacin may be synthesized in the intestinal tract under certain conditions (*c.f.* the synthesis of thiamin (Najjar and Holt 1943) which a maize diet does not favour.

In conclusion, putting aside theoretical considerations one can say that the exact aetiology of pellagra is not yet known but that deficiency of niacin—actual deficiency in the diet deficiency relative to requirements or deficiency due to malabsorption—is the important factor that possibly another factor is associated with maize or other staple food substance and yet another with the patient's individual make up.

**Niacin requirements**—The general opinion that 10 mgm of niacin is the minimum amount required daily is little more than a scientifically based guess. The recommendation that a diet should contain 15 to 20 mgm  $\equiv$  based on the above figure with a margin of safety.

**Niacin in food**—Liver, lean meat, yeast, whole grain cereals, peanuts and green leafy vegetables are the best source of niacin. Milk, eggs and white flour are a very poor source.

**Contributory factors**—A point about which there can be no doubt is the effect of the sun in determining the dermal lesions both their seasonal incidence and their anatomical distribution. It is suggested that the effect of the sun  $\equiv$  purely a matter of trauma and that the skin in its ill nourished

state is particularly liable to damage or to put it another way the fullest effect of the morbid changes due to pellagra will fall on tissues already damaged by ultra violet radiation from the sun by infra red radiation from a fire or by friction of the clothes. Other contributing factors are hard work, pregnancy, hypothyroidism (*vide supra*), and infections.

#### PATHOLOGY

Niacin is an essential factor in the cellular enzyme systems diphos-

directly by niacin deficiency are described below —

**The skin** —The distribution and macroscopic appearance of the lesions are discussed below. The changes are primarily inflammatory and then atrophic. There is parakeratosis of the epithelial layer, increase of pigment in the Malpighian layer followed by oedema and desquamation which leaves the surface red, pigmented and rough. The vessels of the dermis show hyaline degenerative changes.

**Nervous system** —Demonstrable lesions are usually few, but they may be extensive in severe cases and involve the peripheral nerves, cord and brain. The lesions are by no means constant and different observers have described them in different systems. The lesions described include demyelination or even complete Wallerian degeneration of the nerve fibres and chromatolytic degeneration of the cells of the Betz layer, Clarke's column, posterior root ganglia and anterior horn cells. Subacute combined degeneration and atrophy of the cerebrum and cerebral oedema have been described. Leptomeningitis has also been reported but the cerebrospinal fluid seldom shows any changes.

**Alimentary tract** —The mucous membrane of the whole tract including the tongue and mouth shows hyperæmia and sometimes ulceration. This is followed by atrophic changes in the mucosa and also wasting of the muscular coat.

**Other morbid changes** —Death occurs usually from intercurrent disease so that the specific pathological picture is obscured. However there is usually loss of subcutaneous fat and marked muscular wasting, atrophy of the viscera including the heart and degenerative changes in the liver, kidney and suprarenals both cortex and medulla.

**Blood picture** —Some degree of anæmia is the rule. It is usually of the microcytic type but may be macrocytic. Leucopenia and relative lymphocytosis are common findings.

**Biochemical findings** —In the urine there is a marked increase in uroporosein, a substance previously mistaken for coproporphyrin which disappears when successful treatment is given but this substance is also increased in many other conditions (Watson and Layne 1943).

There is usually achlorhydria or marked hypochlorhydria but Castle's intrinsic factor is present in the secretions.

Normally the low limit of about 0.600 mg per 100 c.c.m. in pellagrins is distinctly lower. This is normally about 5 mg per diem. This is decreased in pellagra.

The blood is lower and the urine



Fig 1—Showing the characteristic skin lesions on the backs of the hands and forearms and under the breast.



Fig 2—Showing the separation of the pellagrous epidermis under treatment.



Fig 3—Showing typical lesions on the back of the hands.



Fig 4—The same as Fig 3 six weeks later after treatment.

## SYMPTOMATOLOGY

There is no accurate information about the incubation period, it is

are commonly observed in children should be considered as pellagra

**Onset.**—The first symptoms to appear are variable, but in any one population they will usually be constant (suggesting that the pellagra syndrome, as it is usually seen, is due to a mixed deficiency). The most characteristic symptom is the dermatitis, and, being also a very striking one, it will be the symptom that will most frequently bring the patient under medical attention. Careful inquiry will usually, however, elicit a prior history of lassitude, loss of weight, and gastro-intestinal disturbances and soreness of the tongue and dysphagia. In some cases there is definite mental deterioration before any other signs or symptoms appear. The usual history is one of periods of improvement and then relapse over a period of several years before the full syndrome is developed, although there are instances in which the disease develops more rapidly. It is noticeable that the onset and the relapses or exacerbations occur at one particular season of the year (*vide supra*).

A very large variety of signs and symptoms are attributed to pellagra but it is uncertain how many of these can readily be associated with the central syndrome and how many with other deficiencies. The more specific signs and symptoms can be grouped under the following headings—

**Dermatitis.**—The skin lesions, which are usually symmetrical at first suggest sunburn. There is hyperæmia and œdema, and a burning or itching sensation. The hyperæmia does not, however, clear up as it would in a true case of sunburn, but large scales form which may separate and leave a red rough area with a sharply demarcated pigmented edge. In the acute stage, bullous eruptions may appear.

The distribution of the skin lesions is typical in about 75 per cent of cases they appear on the backs of the hands. Other common areas are on the extensor surfaces of the forearms and arms on the dorsa of the feet (where there are exposed to the sunlight), on the shoulders, collarwise on the back of the neck (Casal's collar), and on the malar eminences (butterfly erythema). These are the areas that are most affected by sunburn.

The dermatitis sometimes extends like a cuff around the wrists and ankles, here it tends to persist leaving a brownish stain on fair skins and permanent depigmentation on dark ones. Other sites are the perineum the elbows and the genital and axillary folds, especially when these areas are subjected to pressure of clothing. Typical lesions are shown in Plate XX.

**The intestinal tract.**—The attention to the mouth is first attracted by difficulty in taking hot and spicy foods. The tongue is a scarlet red (cf. the more magenta or cyanotic tongue of riboflavin deficiency) œdematous and indented and very sore to the touch, it then loses its epithelium takes on the characteristic glazed appearance. There is a general inflammatory condition of the whole mouth with aphthous ulcers along the and on the frimum of the tongue and ulceration of the gums which often infected with Vincent's spirochete. There is increased salivary

to inability or disinclination to close the mouth over the swollen tongue. The pharynx becomes involved in the same process; this leads to difficulty in swallowing and disinclination to take food soon follows. Later the tongue may become completely denuded of epithelium, atrophied and fissured.

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**Nervous:** Tremors of the tongue and face muscles are noted early in the disease and the occurrence of Chvostek's sign (a spasm of the facial muscles on tapping) has been reported; later this extends to other muscles. There are fleeting pains in different parts of the body, numbness and paresthesia. The deep reflexes are exaggerated at first, later decreased and finally lost. Peripheral neuropathy is often very troublesome, but recent work tends to suggest that this may be an associated condition (vitamin B<sub>1</sub> deficiency).

Later mental changes are characteristic symptoms of the disease; there are headaches, sleeplessness, dullness, anxiety, etc.

So called toxic psychosis that develops after a lapse of some time.

**Other signs and symptoms**—The vaginal mucosa is usually red and sore and there may be a vaginal discharge. There is nearly always progressive emaciation. There may be irregular fever but it is not a constant symptom nor is it probably associated with the central pathological and symptomatic syndrome. Anemia is usually very noticeable; this has been mentioned above.

#### DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A typical case presents an unmistakable picture but the other end of the scale there are cases with slight and questionable symptoms that will defy accurate diagnosis except possibly by biochemical and therapeutic tests.

Diagnosis will have to be considered under the following headings—  
(a) **History**—Environment and diet, general and special, duration and seasonal variation of symptoms.

(b) **Clinical picture**—Especially the characteristic dermatitis with glossitis, diarrhoea and mental deterioration.

(c) **Laboratory tests**—Decreased niacin in the urine and in the blood is the rule but the methods of estimating it are very complicated and certainly not within the scope of an ordinary diagnostic laboratory.



(d) **The therapeutic test**—This must be interpreted with reserve all skin conditions are liable to improve by the administration of large doses of niacin but the improvement will not be so dramatic as in pellagra. On the other hand there are some cases that resist treatment with niacin it should be given both orally and parenterally.

The skin condition has to be differentiated from sunburn poison ivy dermatitis trade dermatitis lupus vulgaris lupus erythematosus erythema multiformis and syphilis the gastro intestinal symptoms from nutritional diarrhoeas and sprue (in these there is usually more commonly a macrocytic anaemia, and less commonly achlorhydria and in sprue there is fatty diarrhoea and a flat blood glucose curve on oral administration) and the nervous and mental symptoms from neurasthenia beriberi ergotism lathyrism tabes Korsakoff's and Wernicke's syndromes and general paralysis of the insane.

### PREVENTION

As pellagra is a dietetic disease, its prevention is primarily an economic and educational problem rather than a medical one. However the distribution of specific preventive substances at the worst period of the year and the provision of early medical relief should form part of any anti-pellagra campaign.

Maize is only used as a staple diet because the people cannot get anything better and provided it is suitably supplemented its consumption is not detrimental to health, the aim should therefore be the encouragement of suitable supplementation rather than the radical alteration of the diet.

Much can be done by education and propaganda. It is first necessary to make the people understand the necessity for including certain substances in their diet and many will find the means for doing so if not at first perhaps at least in the course of a few years. Again if they are made familiar with the signs and symptoms of the disease and are made to understand that it is amenable to treatment and if treatment is put within their reach they will probably prevent themselves for treatment in the earlier stages of the disease when its progress can be checked easily.

Naturally methods of improving the economic status of pellagrous populations must be explored but apart of this it may be possible to encourage and even provide the means for home gardening or poultry keeping and at the worst times of the year to distribute dried yeast or even tablets of niacin (100 mg daily) through schools or other channels.

The best supplementary foods are fresh meat especially pork liver whole grain cereals and green leafy vegetables. It may be necessary to fall back on tinned (canned) vegetables fish and meat which will serve the same purpose but less effectively. The principle should be to increase the proportion of protein as well as to provide an adequate amount of vitamin B complex.

In institutions or camps the disease should never arise if the diets are properly designed but in the case of actual food shortages when it may be necessary to fall back on some poorer staple substances such as maize dried yeast should be provided.

Dried yeast autolysed yeast or marmite (vegex) or some similar preparation is also a useful supplement for restricted invalid diets, when

for any reason it may be necessary to restrict other pellagra-preventing foods

### TREATMENT

The treatment of pellagra seldom presents much difficulty, insofar as treatment of the individual moderately-advanced case is concerned, the real difficulty arises in the treatment of large poor populations and here the medical aspects are overshadowed by the economic ones. Treatment can be considered under the four headings general, dietetic specific and symptomatic

**General**—The patient should be removed from the unsatisfactory conditions under which he is living, and put into hospital or at least to bed under good home-nursing conditions. The room should be light and airy, but direct sunlight should be avoided until the patient's reactions to this have been ascertained. Any concomitant infections such as ancylostomiasis or malaria, should be treated and any other dysfunctions, such as hypothyroidism and achlorhydria corrected or compensated.

**Dietetic**—The patient should be given a good mixed high-protein diet, with a calorie value of at least 20 per cent above his normal requirements in which there is fresh meat (including liver or pork) whole-wheat (or other good cereal) meal leafy vegetables and fresh fruit.

**Specific**—In most cases there will be immediate improvement following rest under good hygienic conditions with a good diet but if to this, suitable once for treatment is added the improvement will be more rapid in fraction of the vitamin B<sub>3</sub>. It is best to give large doses—three or four days and then 100 mg daily, until all signs and symptoms have disappeared. Niacin can also be given intramuscularly or intravenously in doses of 100 mg. There are no disadvantages in the intramuscular method and it obviates the danger of non absorption, but not more than 10 mgm should be given intravenously by means of a serum syringe, and even this should be given slowly. If the larger dose is considered necessary it should be given in a pint of 5 or 10 per cent glucose, slowly. Large intravenous doses cause acute peripheral dilation that may be dangerous. Niacinamide does not cause this dilation and may be given in the full therapeutic doses with impunity.

The effect on the skin lesions is immediate and dramatic, the writer has seen an excellent case of pellagra entirely spoilt for teaching purposes, in a period of 48 hours by an ever enthusiastic house physician! But the improvement in the other symptoms may not be so marked. It is very often advisable also to give riboflavin in cases of severe stomatitis and thiamin in cases complicated with peripheral neuropathy, and there are some cases in which liver extract also seems to be necessary, suggesting that this contains yet other specific substances. There are some workers, who, in view of these facts, prefer to treat all cases of pellagra with liver extract parenterally and dried yeast by the mouth. Further, there are some cases in which improvement is only slight and temporary with specific treatment unless this is combined with a general improvement in the diet and especially with an increase in the intake of good protein.

**Symptomatic**—Drugs do not form an essential part of the treatment and in uncomplicated cases complete cure can be effected without them,

but sodium thio-sulphate 7 grains daily, will help the skin condition, and arsenic in the form of Fowler's solution is recommended by some writers. The skin will improve more rapidly if the area is rubbed with olive oil. If there is a hypochromic *anæmia*, ferrous sulphate gr 11, should be given three times a day.

Most of the gastro intestinal symptoms will disappear on the administration of a suitable diet but, if diarrhoea persists, kaolin bismuth or even opium should be tried in turn and, if constipation then supervenes, a mild vegetable purgative should be given for a night or two, and this should be followed by some bowel regulator, such as castor oil, every night.

The stomatitis, if it does not respond to riboflavin, should be treated with a mild antiseptic such as borax and glycerine and if it is painful to the extent of interfering with the taking of proper nourishment cocaine may be added to the mouth application, 2 grains to the ounce. For the mental symptoms and sleeplessness sedatives such as bromides or luminal may be necessary.

### PROGNOSIS

This will naturally vary with the circumstances. If the patient, even in an advanced stage, can be placed under ideal hygienic and dietetic conditions treatment is usually easy and in most cases will end in complete cure but there may be a relapse when the patient returns to his previous mode of life. The disease, however, usually occurs amongst poor populations where the intensity of the symptoms will vary according to the degree of the dietary deficiency, and the usual history is that of improvement during the cold months of the year (in sub tropical climates) with progressively more severe relapses during the summer months of each year.

In a small percentage of cases the patient appears to resist all forms of treatment and after short temporary remissions deteriorates rapidly and eventually dies of some complications.

The death rate in Italy is given as 3 to 5 per cent and in the United States as about 10 per cent, but in some outbreaks in the latter country, it has been placed as high as 30 per cent.

In alcoholics in chronic malarial and dysenteric subjects, and in any febrile state the prognosis is less favourable.

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# SCURVY

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**Definition.**—Scurvy is a dietary-deficiency disease characterized by spongy and bleeding gums and superficial and deep hæmorrhages in different organs and tissues of the body, which if unchecked ends fatally, it is caused by the deficiency of vitamin C (ascorbic acid) in the diet and prevented or cured when it has already developed by the taking of citrus fruits or of other fruits or vegetables containing a sufficiency of this vitamin\*.

**Historical.**—Scurvy was the first dietary-deficiency disease recognized as such its cause was known at least three hundred years before the word vitamin was invented. There is little evidence that the disease was known to the early Greek or Indian medical writers and it seems to have made its debut in the fifteenth century when long voyages of discovery became fashionable. In 1584 Ronseus, a Dutch physician described scurvy and its treatment by means of oranges but did not suggest that lack of them was the cause of the disease. However from this time onwards the practice of carrying fruit and vegetables and even growing the latter on ships to prevent scurvy began to be adopted. In 1747 James Lind carried out his classical experiments which showed that the juice of oranges and lemons prevented the development of scurvy and Captain Cook in his voyages of

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\*The status of scurvy as a tropical disease might well be questioned in view of the fact that several arctic and antarctic expeditions have been marred by its occurrence amongst the personnel nevertheless the inclusion of a short chapter on this disease can be justified on the grounds that whereas the average practitioner in the temperate countries of Europe or America will seldom encounter a case of frank scurvy except possibly in the form of Barlow's disease (infantile scurvy) his opposite number in the tropics may well see a large number of such cases.



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Ascorbic acid is very labile and is very likely to be destroyed by heat and oxygen. It is preserved best in an acid medium, so that the

canned fruit, less than 30 per cent of the original content of ascorbic acid is preserved, but modern canning methods retain much more than this. Again, during storage, of potatoes for example, the ascorbic acid is quickly lost.

Milk is not a good source of ascorbic acid, but, if the cow is fed on fresh grass, her milk will contain far more than if she is stall-fed. Most pasteurized milk supplied in cities is a negligible source of vitamin C. Human milk is a much better source than cow's milk.

When fresh fruit and vegetables are hard to obtain, ascorbic acid can be supplied by sprouting pulses or cereals, unmilled grain is of course necessary. The following method of preparing sprouted grain is given by Aykroyd (1941) —

Grains, such as dal, gram or wheat, or legumes, particularly unsplit peas, are first soaked in water for 24 hours and are then spread out on damp earth or on a damp blanket and covered over with a moist cloth or sack (gunny bag) which is kept moist by sprinkling water upon it from time to time. After two or three days the grains will have sprouted and be ready for use. The sprouted grains should be eaten raw or after cooking for not more than 10 minutes.

#### PATHOLOGY

The deficiency of vitamin C causes an imperfect formation of connective tissue, with failure to develop true supporting tissue, there is not proper adhesion between the cells of the epithelium or the capillary walls, so that these rupture very easily on the slightest trauma or when the internal pressure is increased, and similarly scar tissue does not form properly and is very weak. Osteoblasts fail to differentiate, and there is deficiency of collagenous tissue. The connective tissue is replaced by 'amyloid' connective tissue.

The post-mortem picture will be largely influenced by the secondary deficiencies and the superimposed infections, but a constant finding will be numerous hæmorrhages in most of the tissues and organs, including the brain.

—A microcytic hypochromic anaemia, that responds readily to vitamin C, has been reported, but the writer does not regard any anaemia as due to ascorbic-acid deficiency.

discovery (1772-75) put the principle into practical use for the first time in the treatment of scurvy.

by Holt and Froeh  
and later on the  
Szent Gyorgyi (1933)  
synthesized by Reich

see H. Worth and others

### EPIDEMIOLOGY

(*vide supra*) ever since  
the shorter duration of  
illness. It still occurs in  
India amongst the British

and Indian troops in Iraq during the 1914-18 war. It is very liable to occur in Indian, African or Chinese labour forces working in unfamiliar surroundings as the uneducated labourers are often very conservative and do not eat the unfamiliar local fruits and vegetables. It appears to be the most common specific deficiency associated with famines; it occurred in India during the Hissar famine in 1940 (Nicol 1940).

Sporadic cases not infrequently occur amongst invalids kept on a milk diet and in the form of Barlow's disease amongst infants fed on boiled or preserved milk or on the milk of stall-fed cattle without the supplementation of fruit juice or fresh vegetables.

The disease has no geographical or seasonal limitations and it may occur amongst persons of every race, both sexes and all ages. In certain special circumstances it may exhibit a seasonal incidence just as it may appear to attack certain groups in a population, but the incidence is always explainable in terms of vitamin C intake.

### ÆTIOLOGY

Scurvy appears to be a simple vitamin deficiency disease.

Ascorbic acid which man and other primates and certain other animals notably the guinea pig are unable to synthesize is an essential element for cell metabolism; it must therefore be taken in the food or the organism will suffer. In health the tissues are saturated with this vitamin so that it takes about six months of deficiency before the signs and symptoms of frank scurvy appear. A sub-scurvy state is now recognized, evidence of which can sometimes be elicited prior to the onset of frank scurvy.

The daily requirements of ascorbic acid are 70 to 100 milligrammes for the adult although 30 milligrammes will prevent the development of scurvy. Children require relatively more as also do pregnant and lactating women and persons suffering from fever, malaria, in particular appears to exhaust the ascorbic acid reserves rapidly.

**Sources of ascorbic acid**—The classical and probably the most convenient sources of vitamin C are citrus fruits, especially oranges and lemons, the juice of which contains an average of 60 mg of ascorbic acid per 100 grammes. Other fruits rich in vitamin C are black currants (200 mg), strawberries (50 mg), cape gooseberries (50 mg), pineapples (60 mg), guavas (300 mg), papayas (40 mg) and tomatoes (30 mg). Fresh leafy vegetables, roots and tubers also contain large amounts provided that they are fresh and either uncooked or carefully cooked, notably

Of the laboratory tests the estimation of the urinary excretion of ascorbic acid is the simplest. On a minimum adequate intake of 25 mg, the daily excretion is about 13 mg. There is a sharp response to a test dose of 700 mg if the subject is saturated but if not it may be several days before there is evidence of an overflow in the urine. The urinary ascorbic acid falls to nil in frank scurvy, and no appreciable amount is excreted until at least one gramme of ascorbic acid has been given.

The estimation of the blood ascorbic acid is also relatively simple. If this is as high as 0.7 milligrammes per 100 c.c., it may be assumed that the patient is saturated. A low value does not, however necessarily mean that there is ascorbic acid deficiency.

In differential diagnosis, most of the hemorrhagic diseases will have to be considered, and it may be necessary to make a platelet count and do a prothrombin test.

### PREVENTION

The prevention of scurvy has been practised on ships of the navies and merchant services of many nations for several hundred years often by regulations that make it compulsory to carry fresh fruit or fruit juice for consumption by the crew. In institutions and armies it can be prevented by including in the rations some good source of vitamin C and by training cooks not to destroy such of the vitamin as is present in raw food by overcooking it, or by using copper or brass utensils. When all other sources are precluded it can be provided by sprouting grain (*vide supra*).

The present shortage of shipping has reduced the amount of citrus fruit that can be imported into Great Britain. To replace this deficiency, synthetic vitamin C is being used freely.

Education and propaganda play an important part in prevention. The importance of taking fresh fruit and vegetables or sprouted grain should be impressed on school children and pregnant women in particular the latter for their own benefit and for that of their infants.

As a general rule, the prevention of scurvy is not so much an economic problem as is the prevention of pellagra or even beriberi but this aspect will arise in the case of famines. During the Hissar famine in 1940 powdered ascorbic acid was distributed to the population.

Infants on artificial food or on pasteurized milk should always be given fresh fruit juice daily, this will also apply to infants whose mothers are on a low ascorbic-acid intake and in fact it will be a safe precaution to apply to all infants, as well as to invalids on a milk diet.

### TREATMENT

This presents no difficulties if fruit juice or synthetic ascorbic acid is available. Doses up to 700 mg of L-ascorbic acid should be given by mouth daily for the first 2-3 days and then as tolerated. In severe cases the dose may be given intravenously. The treatment should be continued until the patient is well and then continued for a further 2-3 weeks. This

ciency and recent experimental work has failed to establish the earlier claims

### SYMPTOMATOLOGY

**Latent period**—In infants 'Barlow's disease' usually develops between the sixth and the eighteenth month and similarly in a well saturated adult it is about six months before there is any clinical evidence of the deficiency although in a case in which a partial deficiency has existed for some time the disease may be precipitated within a shorter period

**Onset**—The first signs are pallor breathlessness anorexia and general weakness this is followed by sponginess and bleeding of the gums then swelling so that they almost envelope the teeth which become loose

**Progress**—Large ecchymoses may appear in the skin then subperiosteal hæmorrhages and there may be hæmorrhages into the joints and other serous cavities or even into the brain There may be hæmoptysis and while severe anaemia may come secondarily infected so blood but also it is claimed h drop out and usually the patient becomes progressively weaker and eventually dies of some complication such as pneumonia

In infants the most striking additional feature is the extreme tenderness of the joints so that the infant is terrified when anyone approaches its cot If the knee is flexed and everted a swelling of the lower end of the femur will be seen which is usually symmetrical this is not tender Later the upper limbs may be similarly affected There is also usually radiological evidence e.g. sub epiphyseal hæmorrhage or cessation of the development The spongy gums and other signs will also be present

### DIAGNOSIS

This can be made on (a) the dietetic history (b) the clinical examination (c) the therapeutic test and/or (d) certain clinical and laboratory tests

Frank scurvy will usually present little difficulty from a clinical point of view if there is a dietary history that is compatible with vitamin C deficiency However it is unwise to diagnose scurvy in an adult on a mixed diet or in a breast fed child on clinical examination alone in such cases diagnosis by laboratory tests or at least the  
A good clinical response within a few  
of ascorbic acid constitutes a positive  
also be accepted

A relatively simple clinical test is Gothlin's capillary fragility test a sphygmomanometer band is placed on the arm and the pressure raised to 90 mm of mercury for three minutes the arm below the band is then inspected with a hand lens and in cases of deficiency there will be numerous capillary hæmorrhages No clinical test is however entirely reliable although this is better than Rotter's intra dermal test that most reliable workers have now discarded

## EPIDEMIC DROPSY\*

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**Definition**—Epidemic dropsy is the provisional (and not very appropriate) name given to a non-infectious disease which is characterized by gastro intestinal disturbances œdema of the extremities certain specific skin manifestations and cardiac dysfunction, and is frequently fatal, it has a very limited geographical and racial distribution being confined mainly to Bengal and Bengalees, and its exact ætiology is as yet unknown, but it is undoubtedly associated with food and probably with mustard oil

**Discussion**—This disease has in the past suffered many things of many theorists. It has been fitted into a variety of categories to which it quite obviously does not belong by both local and long-distance investigators who have exalted

\* This is written with the aid of some notes

Chaudhuri his late colleague and cuts whose clinical experience of

is not usually necessary. Infants require 40 mg daily for two or three weeks. When synthetic ascorbic acid is used, it is good practice to supply a natural source of vitamin C in the diet as well, since cases have been reported in which the response to the synthetic vitamin alone was not satisfactory.

Subsidiary treatment is seldom necessary, but the correction of this deficiency may uncover other deficiencies so that a diet rich in all important vitamins should be given whenever possible.

If the specific treatment is given, even in advanced cases, the prognosis is usually good.

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## EPIDEMIC DROPSY\*

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**Definition**—Epidemic dropsy is the provisional (and not very appropriate) name given to a non infectious disease which is characterized by gastro intestinal disturbances œdema of the extremities certain specific skin manifestations and cardiac dysfunction, and is frequently fatal, it has a very limited geographical and racial distribution being confined mainly to Bengal and Bengalees, and its exact ætiology is as yet unknown, but it is undoubtedly associated with food and probably with mustard oil.

**Discussion**—This disease has in the past suffered many things of many theories. It has been fitted into a variety of categories to which it quite obviously does not belong by both local and long-distance investigators who have exalted

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\* The clinical paragraphs of this paper were written with the aid of some notes given to the writer for this purpose by Dr R N Chaudhuri his late colleague and the assistant professor of tropical medicine in Calcutta whose clinical experience of this disease ante-dates the writers by several years.



casual clinical observations of secondary importance—both in this disease and in the diseases to which they have attempted to liken it—to the position of main symptoms and have then in these distorted pictures seen similarities which do not exist in the typical pictures of these two diseases

The two diseases with epidemic dropsy diet of which (admittedly) short latent period, between the writer can see the 'wet' form of beriberi, the similarities are more apparent than real, and between epidemic dropsy have seen any in

Epidemic dropsy dietetic diseases and unique pathology, and fore deserves consideration that at present on population of about 1 of its study seem to

### EPIDEMIOLOGY

**Geographical distribution**—Epidemic dropsy was first reported in Calcutta in 1877 and this city has been the focal centre of this disease ever since. This is primarily because Calcutta is a large town with a very large Bengalee population and because medical and popular attention has been drawn to the disease here. It was reported in Mauritius in 1879 amongst labourers from Calcutta (who probably brought their own food with them or at any rate lived on the food to which they were accustomed, imported from Calcutta), and more recently an outbreak has occurred in Fiji, again amongst labourers imported from Bengal. It frequently occurs in other centres in Bengal and in the neighbouring provinces, Assam, Bihar, and Orissa, and to a less extent in the Central and United Provinces

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**Epidemic status**—Sporadic cases are seldom seen. The disease occurs in small or large outbreaks, involving one family or a large group, e.g. a students' mess or some institution. Several outbreaks will occur at the time, giving the semblance of an epidemic, but such outbreaks will be scattered widely in the locality, and it will usually be impossible to trace any link between any two of them. When the disease occurs in a labour force, it will occur amongst certain groups that feed together

It is a disease of middle-class Bengal families, the entire family, except the infants and young children, is usually affected in varying degrees of severity, and the servants, of which there may be several in a large Hindu joint-family, are usually also involved although they may escape if they have separate feeding arrangements

**Age, sex, race, and economic status**—Suckling infants are never affected and young children up to the age of four years very seldom, the sexes are equally susceptible, as noted above. Bengalees are particularly affected although the disease also occurs amongst Anglo Indians, and others who eat both rice and mustard oil, but it is practically unknown amongst Europeans and Marwaris in Calcutta, neither of which communities use rice as their staple diet, nor mustard oil in cooking, and the poor-

est classes of the community usually escape (These people often cannot afford mustard oil and also they do not throw away their rice water)

### ÆTIOLOGY

During the last sixty years, many theories have been formulated, they have lived their days, become history, and have been revived again

The theories that have been put forward can be grouped as follows —

(a) That it is caused by an infecting organism a bacterium or a virus, that can be passed from person to person,

(b) That it is an intoxication acquired from

- (i) diseased rice
- (ii) mustard oil or
- (iii) some other source,

(c) That it is a food-deficiency disease

(a) Whilst the *infected rice* theory is a possibility from time to time, epidemiological and the mode of origin

(b) Similarly the *food-deficiency* theory will not stand at least not alone, most of the main epidemiological facts are opposed to it. However, people who take milled rice as their staple diet even if this is par-boiled, are not living very far above vitamin B<sub>1</sub> deficiency line, so that this cannot be entirely dismissed as a possible contributing factor

(c) We are thus left with the *intoxication* theory (i) Rice has always been natural that it should as all communities. Acton and Chopra

It was suggested that after par-boiling and milling, if the rice were allowed to get damp in transit, and/or was kept in a damp and airless *godown* (store-room), it was likely to become infected by a gram positive spore-forming bacillus, which, causing degenerative changes in the starch of the rice, produced a central opacity in the rice grain that could be seen easily when this was immersed in water. This degenerated rice when cooked in water-soluble toxin that spread capillary, found in some samples but there were many gaps both on the bacteriological and on the pharmacological side, particularly in the matter of controls in this attractive theory and as such it was received with considerable scepticism

Although the broad epidemiological observations, for example that the disease was virtually confined to rice eating people, were in favour of any *rice* theory, and sometimes amateur local enquiries seemed to suggest that certain supplies of so-called 'diseased' rice might be responsible for some of the outbreaks, no expert epidemiological investigation has been carried out prior to 1935. Discussing the problem in an editorial in the *Indian Medical Gazette* of December 1935 the present writer commented —

'The epidemiological investigations must be raised from the anecdotal to the scientific level. The population subjected to enquiries must be a large one and only selected on a geographical, not on an economic social or religious basis, the enquiries must be made amongst those who have not as well as those who

have suffered from the disease, the mild cases of the disease must also be taken into account, and this presents difficulties as it means that a careful medical examination of the whole population at the time of the outbreak is necessary, histories taken at a later date may be misleading. Very few investigations of this nature have been undertaken but it is only through such investigations that we are likely to reach a solution of the problem.

**Recent work.**—An epidemiological investigation was undertaken by Dr R B Lal, the professor of epidemiology and vital statistics at the All-India Institute of Hygiene, Calcutta, and his staff, in six different areas, in Bengal, Bihar, and Assam, including a tea-estate, where an outbreak of the disease had been recognized and reported by Dr Charles Terrell. These investigations appeared to point once more to mustard oil as the probable vehicle of the noxious factor, and the same workers, in an investigation conducted with the clinical collaboration of members of the staff of the Calcutta School of Medicine, were able to produce suggestive symptoms in volunteers fed on samples of mustard oil that had come under suspicion in epidemic dropsy outbreaks (Lal *et al* 1937-41).

During the last half century mustard oil has been suspected repeatedly but in 1926 Sarkar recorded an outbreak in which several patients had all the symptoms of severe epidemic dropsy after taking oil that had been contaminated with argemone oil (from the seeds of *Argemone mexicana* local names *salkata* or *katakhar* oil). In 1928 Kamath, reporting an outbreak in which mustard oil was taken and applying his data to support the infection theory, noted that oil from a seed, known locally as *odissimari*, was also used, this seed has now been identified as *Argemone mexicana*.

Attention was thus directed to a specific contaminant of mustard oil and feeding experiments were carried out at the Calcutta School of Tropical Medicine on human volunteers and on animals (Chopra, *et al*, 1939) with very suggestive results.

We have now arrived at the position in which mustard oil has been incriminated once more, but on this occasion the case against it rests on a much sounder basis. — Vital evidence. Argemone oil, a common adulterant, has been shown to produce symptoms identical with epidemic dropsy whether it is administered deliberately or whether it is administered accidentally. A number of recent outbreaks, it has been found that the mustard oil used by the victims was badly contaminated with argemone oil and that when its use was discontinued the outbreak subsided.

We know that argemone oil contains a noxious agent, but up to the present time chemists and pharmacologists are not agreed as to its exact nature, or how it acts, whether it is an independent poison that produces its ill effects, gram for gram according to the dose in which it is taken, or whether the substratum is an important factor and the degree of toxicity depends on the excess of one food substance in the diet or on the absence of another.

Argemone oil is not an adulterant in the sense that it is often added to the oil by the retailer, deliberately for the sake of increasing his profit, but it is an accidental contaminant of the mustard crop as it grows in the field, it is a self-sown weed which can be distinguished easily from the mustard plant when the crop is harvested, and although the seeds are very similar, they could be picked out by a careful farmer.

It is quite understandable that some years would be more favourable to the weed than others and that its percentage incidence in the crop will

vary from place to place, but apparently it is a very common contaminant and a large number of samples of oil show its presence, so that it is easier to account for the wide prevalence of the disease than it is to understand why it is not more prevalent. It is for example not quite clear why epidemic dropsy is comparatively rare amongst the poorer Anglo Indian community who use mustard oil for cooking almost exclusively. Does it depend on the amount of argemone oil present? Irl and his coworkers (1941) place the maximum safe amount at 0.5 per cent. Is it simply because it is heated and partly inactivated or is it something to do with the general composition of their diet in which rice does not preponderate to the extent that it does in most Bengalee diets?

There has long been a strong belief prevalent amongst both patients and doctors that rice *per se* is bad for an epidemic dropsy patient; this belief is independent of the rice-toxin theory because it applies to any form of rice sound or diseased. Dr Ellis C Wilson studying cases in the hospital of the Calcutta School of Tropical Medicine noted that there was a distinct increase in the oedema whenever an epidemic dropsy patient was given a rice diet. There is therefore some evidence that people who live on a diet consisting largely of rice possibly by virtue of its high carbohydrate/vitamin B ratio are more susceptible to the disease and that rice though not the main culprit or the vehicle of the noxious factor does play a part in the aetiology of epidemic dropsy.

In the study of vitamins the idea of conditioned toxicity is now gaining ground: there are numerous examples reported of the toxic effect of a toxic substance being conditioned by the nature of the diet and/or the state of vitamin saturation of the subject *e.g.* selenium poisoning and a high protein diet; lead poisoning and vitamin C; and indol and vitamin B. Is this possibly another such example? Such an hypothesis would provide a means of co-ordinating some of the earlier theories regarding epidemic dropsy: with the latest one, for specific food deficiency was visualized as a possible cause long before the present vitamin age.

Both the clinical and the pathological evidence (*vide infra*) support the epidemiological and experimental evidence and indicate that the disease is far more likely to be due to an intoxication than to either an infection or a vitamin or other food-deficiency.

To summarize, epidemic dropsy is apparently caused by the consumption of some toxic substance in mustard oil probably a constituent of argemone oil, a common contaminant of mustard oil; the effect of this toxin is enhanced if the diet is predominately a rice one.

#### PATHOLOGY

The characteristic pathological change is a persistent dilation of the smaller blood vessels, not simply of the capillaries in all the layers of the skin, in the heart muscle, and in other organs and tissues associated with slight perivascular infiltration by large mononuclear cells, increased permeability, and local oedema. The toxin appears to have a direct specific action on small blood vessels.

These changes can be seen in all the layers of the skin, and in the subpapillary plexus there is often new vascular formation which may progress to the development of hamangiomatous condition that gives rise to the so-called 'sarcoids'. There is often increased pigmentation in the basal layer, and some pigment will be seen in the deeper layers of the skin.

There is œdema in the corium, where the collagen fibres may be swollen, and in the subcutaneous tissue. The 'sarcoid' is a vascular tumour, with few connective tissue cells, no fibroblasts and no inflammatory cell exudate, covered by a flattened epidermis which shows thickening and down growth deep into the normal corium at the edge of the tumour.

In the heart, there is marked vascular dilation between the muscle fibres so much so that sections sometimes give the appearance of free extravasations of blood that have dissected out individual muscle fibres or bunches of fibres.

In the eyes, there is great engorgement of the uvea which results in over production of aqueous humour, increased tension in the anterior chamber, and glaucoma.

**The blood picture**—There is usually a distinct normocytic orthochromic anemia which is apparently due to depressed hæmopoietic function (Napier and Sen Gupta 1940). The leucocyte count is usually slightly raised and there is a shift to the left in the Arneth count. The erythrocyte sedimentation rate is increased considerably.

The urine shows no constant changes, there is however frequently a trace of albumin.

#### SYMPTOMATOLOGY

The latent period between the consumption of the noxious material and the onset of the first symptoms (this can sometimes be estimated with a fair degree of certainty but of course at other times not) is very variable from two or three days to two or three weeks. It is probably dependent on the dose taken. Similarly the onset may be sudden or insidious, again this probably depends on the same circumstances. It is usually possible to obtain a history of nausea, loss of appetite, and looseness of the bowels for a few days, with this there may have been irregular fever but there is seldom much fever by the time the patient reaches the hospital though the diarrhoea often persists.

In the acute cases breathlessness on the slightest exertion, swelling of the feet which is much worse towards the end of the day, and in some outbreaks skin manifestations will develop rapidly. The pulse rate is usually rapid and may be very irregular the blood pressure is variable. In very severe cases, the heart condition progresses rapidly and the patient, now confined to bed, is orthopnoic, or he may die suddenly before the full seriousness is appreciated. <sup>short</sup>ness of breath will persist as <sup>■</sup> diet but will subside rapidly under <sup>mia of</sup> the skin may subside, leaving the sarcoids.

Finally all the more acute manifestations subside and as long as the patient remains in bed, he feels perfectly well but he may be left with a weakened myocardium which prevents him from returning to full work for many months. There are, however amongst better class patients many whose cardiac condition appears to be normal, but in whom a cardiac neurosis develops that is even harder to cure than any true cardiac dysfunction.

Some of the symptoms will be considered in a little more detail.

The œdema, which is both central and peripheral in origin, is almost constant symptom but variable in degree and very rarely general anasarca develops.

The cutaneous manifestations are very common in this condition and apparently run in cycles. In 1922 (1) a 2-year-old girl in the School of Tropical Medicine in London, who had been in the tropics, attracted special attention because of the fact that her skin was covered with more than 1000 small, raised, red, papular lesions. These lesions were distributed over the entire body, but were particularly numerous on the face, neck, and upper extremities. The lesions were particularly the same, a potential cause and the same effect.

The "sarcoid" quality mentioned in the literature is a quality to which Boeck's term "sarcoid" and even the term "sarcoid" is not applied. A "sarcoid" is a term which is applied to a group of diseases of the size of a pin's head to that of a fist, and which are characterized by the fact that they are easily infected and are liable to recur after removal.

The heart.—This is frequently enlarged and is a common cause of death due to relative mural incompetence and to a structural dilatation of the heart, due to extension of the tumor into the heart and to the fact that a pulmonary artery aneurysm may develop. In severe cases there are signs of congestive failure.

The electrocardiogram records a normal rhythm, but a marked tachycardia of some origin and extension is in the majority of cases. The P-R interval has been found to be abnormally long in a few patients in the cases investigated, and an abnormal T wave and sinus tachycardia have been found. Orthostatic hypotension frequently occurs and the heart is enlarged especially the left ventricle and the right atrium.

Other symptoms.—Patients of an advanced stage of the disease complain of a burning sensation and of various pains all over the body, but not of a definite "neuritic" paroxysm, or areas of anesthesia. The skin may sometimes appear to be thick at first and later poor, even for the most cases there is little deviation from normal in skin reflexes. These symptoms may of course be due to associated changes in the skin.

Glaucoma develops in about 5 per cent of cases. There is early complaint of rainbow haloes around a light source and then progressive contraction of the visual field and, if untreated, eventual complete blindness. There is usually little pain but on examination the increase in tension will be obvious.

Abortion is the rule in pregnant women.

### DIAGNOSIS

This is based on the clinical picture and the close relation. If several members of a family give a history of acute arthritis followed by edema of the legs, with or without flushing which is warm to the touch and shortness of breath on exertion, careful enquiry should be made regarding the diet of the family, and other members should be examined and questioned for minor signs of the disease.

The characteristic edema and erythema is not matched in any other condition nor are the so-called sarcoids, though these are somewhat like the eruption in verruga peruana (another local disease that occurs occasionally, especially on the nose and side of the globe). The disease has been described in the literature as a "sarcoid" and there is some evidence that it is a form of sarcoidosis. In the present case, the disease is characterized by the fact that it is a disease of the endocrine system and is not a disease of the skin. Between

epidemic dropsy and the 'dry' form of beriberi with its gradual onset, wasting and weakness, and pronounced neuropathies, there are no points of similarity to be discussed. In the 'wet' form, the latent period is again longer than that of epidemic dropsy, the oedema often disguises underlying wasting and neuropathies, and is 'cold', that is unaccompanied by hyperaemia; there are no other cutaneous manifestations, and in the heart condition there is very frequently a dramatic response to the administration of thiamin chloride. All these points taken together will usually make it easy to distinguish even isolated cases, and, when there is a group of cases, should make confusion impossible.

### PREVENTION

It is obvious that this will depend on the final verdict on the cause of the disease, but the present state of our knowledge certainly justifies the adoption of public health measures aimed at the prevention of the contamination of mustard oil by argemone oil, even as an experimental measure.

Preventive measures must be started with the agriculturist to whom the danger of weed should be pointed out, and the seed should be sown on him indirectly, condemning a seed of *Argemone mexicana*, or even by testing the oil that is supplied to the retailer. But there are technical difficulties about the latter procedure in the nitric acid test\*, which has up to now been relied upon for detecting contamination, is not entirely specific.

An interesting observation was made by Tricell (personal communication) namely that in some northerly districts of Assam the mustard and the *Argemone mexicana* do not ripen coincidentally, so that the latter seed is not harvested in these districts, the mustard oil is never contaminated, and epidemic dropsy does not occur.

As far as the individual is concerned the only advice one can give is to warn him to buy his oil from a safe source and/or to have it tested.

### TREATMENT

This is essentially symptomatic and dietetic; no specific is known.

Rest is the first essential, even if the cardiac symptoms are not prominent as, until the patient has been placed on his new dietary regime for

of returning

The diet will depend on the symptoms to some extent, but, if there are no contra indications, a well-balanced diet containing at least the full quota of protein and from which rice and mustard oil are excluded, should be given. Bread or *chappatis* should be given in the place of rice. If the diarrhoea persists this may be stopped by placing the patient on milk or even lime-water and albumin water may be necessary for a few days, but

\* About 10 c.c. of the oil is shaken up with an equal quantity of colourless nitric acid; after two minutes a yellow or reddish brown layer appears at the bottom of the test tube. The test is reported to be roughly quantitative and to detect about 1 per cent of argemone oil.

care must be taken not to keep up this restricted dietary for too long and if there is much oedema, so much fluid may be contra indicated. In the latter case salt also should be restricted.

**Drugs**—An initial purgation with two drachms of liquorice powder at night followed by two or three days of castor oil emulsion (a drachm to the ounce), or one drachm of sodium sulphate, every two hours for the first day and every four hours for the next two days will help to control the diarrhoea and to some extent the oedema but if after this the former persists bismuth and opium should be substituted.

A mixture containing tincture of ephedra 20 to 30 minims and 10 to 15 grains of calcium lactate thrice daily, is prescribed as a routine procedure at the Calcutta School of Tropical Medicine theoretically because ephedrine is vaso constrictor and a circulatory stimulant at least patients appear to do well on it. A diuretic e.g. diuretin grs 10 is added if there is any oedema. If the oedema is more extensive ammonium chloride grs 10 is given three times a day and then an injection of one of the mercurial diuretics such as neptal or mersalyl. For congestive heart failure digitalis in adequate doses should be given and in severe cases venesection may be advisable.

**Complications** must be treated as they arise the fluid may have to be removed from serous cavities. Glaucoma must be watched carefully and if there is no improvement with general treatment and the visual fields tend to diminish, trephining or anterior sclerotomy may be necessary.

#### PROGNOSIS

Even in the mild case the patient is not really fit for manual work within three to four weeks in the moderately severe case with any evidence of cardiac involvement he will not be fit to resume even clerical work within this period and, in the severe case the patient will be incapacitated for several months.

The death rate in an outbreak will usually be about 5 per cent but in some severely affected families half the members have died. Death is from heart failure.

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## LATHYRISM

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**Definition**—Lathyrism is a syndrome of which the most prominent clinical feature is muscular weakness and later spastic paraplegia. It occurs especially during times of drought and famine amongst certain population groups whose staple diet is a vetch *Lathyrus* in India, Spain and elsewhere.

**Historical**—The condition was recognized as a dietetic disease by the early Indian medical writers and later by Hippocrates. In the 17th century it was definitely associated with the eating of the vetch *Lathyrus* from which it derived its name and in some European countries edicts were proclaimed forbidding its use. In India the condition was reported early in the last century by several British physicians and since then outbreaks have occurred frequently.

### EPIDEMIOLOGY

The disease has appeared in several European continental countries including France, Italy, and Spain (in Barcelona, Cuenca, Ciudad Real, Toledo, Valladolid and Madrid provinces) in North Africa, Abyssinia, Iran and in India (the Central and United Provinces, Central Indian States and Bihar in particular). In North Rewah (Central India) in 1921 it was estimated that 6 per cent of the total population of about a million people were affected. There have been a number of recent reports of the condition in Spain (Jimenez Diaz *et al.* 1943 and Martinez Almeida 1943).

The persons most affected are males between the ages of 15 and 30 that is during the most active period of their lives.

It is a disease of famine years and it occurs almost exclusively amongst members of the lowest economic classes but the individuals affected are often well nourished since the vetch provides a diet of high caloric value.

## AETIOLOGY

The actual cause of the disease is still in doubt. It is not a pure deficit with and the deficit is incriminated but in other countries *L. cicera* and *L. clymenum* are the common vetches used.

On the other hand, it is almost certainly not a pure food intoxication for the vetch is used by many people as a staple diet and by a much wider group as an additional item in the diet without causing any of the symptoms of lathyrism.

There seem to be three possibilities

(a) That it is caused by toxins derived from *Lathyrus sativa* which has been grown under certain special conditions or which has undergone certain changes after harvesting through having been kept in damp storage for example.

(b) That it is due to contamination of the *Lathyrus* crop by some other vetch e.g. *Vicia sativa*, locally known as *akla* that is not easily distinguished from *Lathyrus sativa* and which either normally or under special circumstances is toxic.

(c) That the disease is a conditioned toxicity that is to say the pathological changes are caused by a toxin in *Lathyrus* or less probably in some common contaminant of the *Lathyrus* crop in the absence of some vitamin or other food factor that normally neutralizes its effect. This has for some time been the present writer's interpretation of some of the apparently contradictory observations regarding the aetiology of this disease in India, the recent work of Jimenez Diaz and others (1943) in Spain seems to provide considerable support for this hypothesis.

Toxins were isolated from the germinating *Lathyrus sativa* by Acton and Clowes (1922) and from *Vicia sativa* var. *argus folia* Howard by Simon and Anderson (1922) have isolated a toxic base dissolving in the central nervous system in experimental evidence in other the contaminating

By feeding monkeys on pure samples of lathyrus peas Stockman (1929) in Glasgow produced a temporary spastic paralysis that was very similar to the more permanent condition lathyrism observed in man. Geiger, Steenbock and Parsons (1933) produced lathyrism in rats by feeding a diet on the seeds of the higher the peas not prevented but

Lewis and Esterer (1943) produced a similar condition in rats by the cold water extract of the sweet peas.

Jimenez Diaz et al. included that the condition is due to the exclusion of other dietary substances with the lipid fraction and that the condition is not a vitamin deficiency but that if taken in sufficient amount will antagonize the vetch toxin. This antagonistic substance is not a vitamin and can apparently be synthesized by some animals (but not by man or the horse) and is present in most food of animal origin.

The horse is apparently the only other mammal commonly affected in nature.



taking the body-weight in the hands and balls of the feet and shuffling the buttock forward

### PREVENTION AND TREATMENT

All measures to discourage the use of *Lathyrus* as a staple diet should be taken. These will amount to anti-famine measures by irrigation schemes and by a better distribution of other staple foods during periods of drought for example. Much has been achieved on the c lines in recent years in India. When the toxic substance and/or the hypothetical antagonistic substance have been identified it will probably be possible to take more specific measures but it has been shown that a high protein diet largely of animal origin will usually arrest though not reverse, the pathogenic processes. There is little evidence that any improvement can be obtained by treatment when paresis has developed.

### PROGNOSIS

The vital functions are not involved and the expectation of life is not directly affected but the patients who are mostly of the uneducated agricultural class, become dependent on charity for their subsistence.

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# INFANTILE CIRRHOSIS OF THE LIVER\*

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**Introduction**—In private practice, more than in hospital practice in eastern India it is not uncommon to encounter children with a definite enlargement of the liver for which no obvious cause is found. The enlargement is usually associated with irregular fever, jaundice, and enlargement of the liver soon after birth.

## EPIDEMIOLOGY

**Incidence**—Hospital reports in India do not usually reflect the true state of affairs, as parents will not bring their children to hospital. In a series of 1,100 children investigated by Rao (1934) in Vizagapatam, the incidence was 28 (or 2.5 per cent) in the figure 1,748 for the years 1933 and recent Calcutta figures show 300 deaths a year. It is more common in urban than in rural populations.

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**Geographical distribution**—The disease is particularly common on the eastern side of India, in Bengal, Madras and Mysore, but cases are reported from Bihar, Orissa, and the Central and United Provinces. It is not seen in full station.

**Age, sex, race, and social status**—Children between the ages of six months to two years (the dentition period) are most commonly affected, but the disease is sometimes seen in older children.

Children of both sexes are affected but possibly there is a slight male predominance. It is popularly said that the first male child after a series of females is likely to be affected, the explanation might be that it is the most pampered child who will be likely to have artificial and unsuitable food pressed upon it.

The disease has a remarkable predilection for the Hindu community, and is most common amongst orthodox Hindus who are strict vegetarians. In the series of 1,748 cases referred to above 1,616 were in Hindus, and Narayanamurthi and Tirumurthi (1939) reported a series of 445 cases in which none were either Mohammedans or Anglo Indians.

The vast majority of the children come from middle class families.

**Heredity**—There is a strong indication of an hereditary tendency. It is usual for several children in the same family to suffer as each reaches the crucial age.

#### ÆTIOLOGY

This is obscure. Inherited predisposition and defective feeding are the most important factors. There is a high incidence of repeated child-births, and an excessive use of sweets and the child's health. The artificial feeding is started early and sweets and fats (buffalo milk) are given. The vitamins are not considered and the protein intake is low. The child suffers from gastro-intestinal upset and the toxins that are absorbed are not properly dealt with by the liver. Possibly an inborn error renders the liver cells peculiarly vulnerable to toxins and/or dietary (protein) deficiency, and they undergo premature degenerative changes.

#### PATHOLOGY

As a result of the toxic action and/or disordered metabolism, there is fatty infiltration and later the liver cells become necrosed and are absorbed. The healthy cells multiply to replace the lost and there is also a secondary fibrotic change commencing in the centre of the lobule. The fibrous tissue develops within the lobule between the cells (intercellular cirrhosis). With the regeneration of the liver cells, there is also formation of new biliary channels. In the advanced stage portal cirrhosis supervenes with the resultant ascites and jaundice.

**Blood Picture**—There is a very distinct microcytic anemia and a pronounced leucocytosis. The latter is usually between 15 and 20 thousand per cmm but the normal proportions of the differential count are maintained.

#### SYMPTOMATOLOGY

The onset is insidious. During the prodromal stage the child, although appearing well-nourished, becomes peevish, irritable, and refuses food. He

lower normal levels of hæmoglobin often existed. Figure are given from a manganese mine where malaria was endemic and from tea estate labour forces where both hookworm infection and malaria were prevalent; the subjects were ordinary workers selected at random after the grossly (clinically) anæmic individuals had been excluded. The manganese mine recruits were mostly undernourished but showed no heavy parasitic infection.

### THE CAUSES OF ANÆMIA IN THE TROPICS

From the data given above it will be clear that climate *per se* does not cause anæmia. What then are the causes of anæmia in the tropics? This anæmia varies in its degree and nature in much the same way as does the anæmia that occurs in temperate climates and it is susceptible to classification along the same lines.

**Classification of anæmia**—The causes of anæmia will be appreciated

tion of the average man there are about twenty five million million red cells and the duration of the life of a red cell is probably on the average about 75 days which means that in order to maintain the circulating red cells at a constant level about three hundred and thirty three thousand million new red cells have to be produced by the hæmopoietic tissues daily to replace the three hundred and thirty three thousand million obsolete ones that disintegrate or are otherwise withdrawn and disposed of by the hæmolytic tissues. Production and destruction have to be balanced and any to be made good. The body is capable there is failure of production if there is excessive destruction anæmia must eventually result.

Deficient anæmia may be caused by (a) errors of erythrogenesis (b) loss of circulating blood or (c) errors of erythrolysis and it will be convenient to classify the causes of anæmia under these three major headings.

The following table (Napier 193 of the anæmias in general with examples the anæmia of each particular group cosmopolitan diseases but wherever included.

**Specific causes of anæmia in the tropics**—These are (a) infections (b) dietary deficiencies or more commonly a combination of these two causes and (c) congenital defects. It will be convenient to consider the subject under these three headings with the full appreciation of the fact that the division is an artificial one.

In the appropriate places in this book reference has usually been made to the blood picture in the diseases in which anæmia is a prominent symptom but it will be worth reconsidering the subject here.

### ANÆMIA DUE TO INFECTIONS

**Malaria**—This is probably the most important source of anæmia in the tropics. The most obvious cause of the anæmia is the destruction of the red cells by the parasite that is it is a hæmolytic type of anæmia due to the error of erythrolysis III A (iv) in the above classification but there

A Classification of the Anemias

Main groups	Sub-groups	Examples of syndrome	General character of blood picture etc.	Principal treatment
I	A Aplastic or hypoplastic of toxic or mechanical origin, due to— (1) unknown causes (2) (a) bacterial or other parasitic toxins (b) metabolic toxins, (c) chemical and physical poisons (d) mechanical interference with blood formation (e) exhaustion of the bone-marrow	Idiopathic aplastic anaemia Anaemia of many acute and chronic types including tropical diseases, e.g. relapsing fever and malaria fever Anaemia of nephritis Anaemia caused by benzol, lead, sulphur, phosphorus, radium and x-rays Carotomatosis—Albers-Schoenberg disease Terminal condition in many hyperplastic anaemias	Usually normochromic reticulocytes—few van den Bergh—negative urobilin—absent	Remove cause Transfuse to tide over critical period and next time re-accumulate blood cells to supply needs
	B Nutritional dysplasias— (1) iron deficiency (a) Actual (b) Relative (c) Failure of absorption	Hypochromic anaemia of infants and adults and others Hypochromic anaemia of pregnancy and hookworm infection Simple achlorhydric anaemia	Microcytic hypochromic reticulocytes few van den Bergh—negative normoblasts present urobilin—no increase	Supply excess of iron by mouth Ferrous sulphate gr. xv daily for three weeks
	(1) Deficiency of haemopoietic principle (a) Absence of intrinsic factor (b) Absence of extrinsic factor a) Actual b) Relative or conditioned (c) Failure of absorption (d) Failure of storage (e) Failure of utilization (2) Deficiency of vitamin B <sub>12</sub>	Idiopathic pernicious macrocytic anaemia Typical macrocytic anaemia of pregnancy Anaemia of sprue Anaemia of liver disease Acquired anaemias Hypochromic anaemia of vitamin B <sub>12</sub> deficiency	Macrocytic hyperchromic (a) reticulocytes + megaloblasts van den Bergh + achlorhydria (b) van den Bergh—negative and reticulocytes—few	Supply deficiency of vitamin B <sub>12</sub> by liver extract (a) Refined liver extract parenterally or liver by mouth (b) Crude liver extract and mineral
	(1) Deficiency of vitamin B <sub>12</sub>	Idiopathic pernicious macrocytic anaemia of vitamin B <sub>12</sub> deficiency	Macrocytic hyperchromic (a) reticulocytes + megaloblasts van den Bergh + achlorhydria (b) van den Bergh—negative and reticulocytes—few	Supply deficiency of vitamin B <sub>12</sub> by liver extract (a) Refined liver extract parenterally or liver by mouth (b) Crude liver extract and mineral

ANEMIA  
OR  
ERYTHRO-  
GENESIS



## 4 Classification of the Anemias

Main groups	Sub-groups	Examples of syndrome	General character of blood picture, etc	Principles of treatment
II  LOSS OF BLOOD FROM CIRCULATION SECONDARY ANEMIA	Due to hæmorrhage, external, from mucous surfaces, or into serous cavities			
	A Following external or internal injury	Severed artery, ruptured spleen, etc	The blood picture will depend on whether the hæmorrhage is acute or chronic <i>Acute</i> normocytic normochromic reticulocytes + +	Stop bleeding and remove cause where possible  Transfusion
	B Associated with disease of tissues	Hæmorrhoids, gastric ulcer, hæmoptysis, dysentery—amoebic, bacillary or metazoal, vesical schistosomiasis	<i>Chronic</i> microcytic hypochromic reticulocytes + or ± van den Bergh—negative normoblasts present urobilin—no increase	Supply iron in excess and give good protein and vitamin diet
	C Associated with hæmorrhagic states	Scurvy, snake (asper) bite		
	D Associated with blood sucking parasites	Hookworm, leishmaniasis		
III  ORGA NOLYSIS	A Conditions affecting red cells and making them more susceptible to normal lytic processes (i) Abnormal red-cell structure, (ii) Abnormal physical condition of red cells, e.g. spherocytes, (iii) Effect of toxins, chemical poisons, etc., (iv) Parasitization	Sickle-celled anemia Achloric jaundice, paroxysmal hæmoglobinuria Lead poisoning arsenical drug poisoning Malaria and <i>oroja fever</i>	Normocytic or slightly macrocytic normochromic reticulocytes + + + van den Bergh + + + urobilin + + + increased fragility of red cells	When known and when possible remove cause, e.g. malaria parasites by specific treatment. Provide hæmopoietic substances in food, protein, vitamins and liver fraction
	B Conditions causing overaction of the erythrolytic tissues	Chronic nodular splenomegaly, possibly kala-azar	disile decreased fragility of red cells	Remove cause in chronic splenomegaly remove spleen

is evidence that the animals in the water were in the blood stage, as shown by the same additional explanation for the same animals as in the first observation, except that there is a time interval between blood and plasma as long as the malaria infection is incubated so that it is not yet detectable as a toxic hyperaemic anaemia. I have to mentionable XXX

Further when there is very extensive red cell destruction especially if the patient has been repeatedly subjected to these attacks the blood forming material stored in the body becomes exhausted. Most of the iron is stored and re-utilized but some of the other hemopoietic elements apparently need replacement, in such cases a microcytic anemia sometimes develops which does not improve spontaneously as the anemia of malaria usually does once the infection is under control but responds immediately with a sharp reticulocytosis when liver extract is given. This would bring the anemia into the group of relative or conditioned nutritional dysplasias I B (n) (b) (d).

It is frequently stated that the anemia of chronic malaria is a hypochromic microcytic anemia. While the writer believes that this is largely a misconception through the frequent association of chronic malaria with other anemia producing conditions e.g. hookworm disease and dietary deficiency, there is one possible source of iron loss that should not be overlooked namely, the fixation of hematin in the form of insoluble haemozoin pigment. It is therefore possible that in some persons on a low-iron intake this source of loss may upset the iron balance and introduce an iron-deficiency element into the anemia. I ■ (1) (b)

Finally, in certain persons subjected to malarial infection for many years through constant stimulation there is an overgrowth of the lymphatic tissues in the body *e.g.* in the spleen leading to a constant excessive destruction of red cells, this places the anaemia in group III B.

One might expect the anemia of blackwater fever to show an iron deficiency element in view of the loss of hemoglobin that occurs through the kidneys, apparently however the amount thus lost if it is insufficient to do irreparable damage to the kidney and kill the patient does not constitute a serious iron loss so that this element in the anemia is overshadowed and a macrocytic anemia that often necessitates the administration of liver extract (the conditioned nutritional dysplasia mentioned above) is the more usual result of a blackwater fever attack.

It is thus apparent that the anemia of malaria is very complex and it is perhaps not surprising that writers have been reluctant to commit themselves to a clear cut statement as to what is the characteristic anemia of this disease.

In the malarial attack in the partially immune there is often little evidence of anaemia which suggests that some immunity to the malarial 'toxin' develops. If such a person is given specific treatment for the malaria immediately, the anaemia can usually be ignored. However, in the non immune adult and in children anaemia is fairly constant.

<p>" " "</p>	<p>- vary with the circumstances attack that is not brought reduced by as much as two - in a blackwater fever attack " " far more gradual and seldom</p>
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% extreme

In the well nourished person with an acute malarial attack return to normal is usually spontaneous once the red cell destruction and the toxin production ceases. When in such a case the hæmoglobin fails to return to normal and there is a persistent reticulocytosis an early relapse of malaria may usually be anticipated the recognition of this residual anæmia is sometimes of diagnostic value when malaria parasites are scanty. In the ill nourished and debilitated it may be necessary to supply some of the blood forming elements in the form of liver extract marmite and even iron to ensure an early return to normal. If the patient has been subjected to repeated attacks over a long period the hæmolytic tissues are hypertrophied and disorganized and in order to adjust the dyscrasia and balance hæmopoiesis whole liver principle (crude liver extract) may have to be given as in the previous case. Finally in extreme cases it may be advisable to remove or put out of action a large portion of the reticulo endothelial system by removing the spleen or tying the splenic artery.

**Ancylostomiasis**—This is probably the second most important source of anæmia in the tropics. The cause is almost entirely blood loss from the bowel as a result of the profligate blood sucking by the adult worm this makes it a true chronic secondary anæmia II D which is usually markedly microcytic and hypochromic. In heavy infections no amount of dietary iron is sufficient to compensate the iron loss but in moderate infections the loss of blood is such that it could be compensated if the individual were on a good iron intake but when the subject is taking a diet containing only the minimal iron requirements this extra loss is sufficient to upset the balance and produce an anæmia that can be classed as a conditioned iron deficiency anæmia I II (a) (b).

Even when an excess of iron is given however there are some instances in which the hæmoglobin level does not reach normal so that there is possibly a toxic element also in this anæmia which would place it in group I A (ii) (a). The degree of anæmia may be very extreme and there are few conditions other than ancylostomiasis and hæmorrhage that will produce a microcytic hypochromic anæmia of this degree when the hæmoglobin is as low as 2 grammes per 100 ccm in a patient obviously not in extremis the infection should always be suspected.

Return to the normal hæmoglobin level follows adequate iron administration even without worm removal except in the few instances referred to above. The worms must however be removed or the anæmia will return (see ANCYLOSTOMIASIS).

On the other hand the activity of the macrophages is stimulated so

Under specific treatment for kala azar the reticulocytes return to normal and there is a steady improvement in the blood picture but the

normal may not be reached for several weeks. The administration of hæmatinics does not usually cause any material increase in the rate of improvement.

(iv)

**Trypanosomiasis**—Anæmia is not usually marked in the early stages of the disease and any anæmia that occurs is probably of toxic origin. In the later stages in the native patients it is often very striking and is certainly mainly nutritional in origin. This class of patient becomes lethargic and indifferent to his dietary needs and lacks the energy to work to earn his food.

**Acute febrile conditions**—The mechanism of the anæmia is not very clear in most of these conditions though a degree of anæmia is common. One must conclude that the anæmia is mainly due to a toxic hypoplasia.

I A (ii) (a)

It may be this and it

In *yellow fever*, *Heil's disease* and *relapsing fever* again anæmia is not usually prominent. The jaundice that occurs is not hæmolytic in origin but hepatic and it is due to the failure of the damaged liver cells in disposing of the products of the normal quota of destroyed red cells. Such anæmia as occurs must also be toxic in origin.

In *brucellosis* the anæmia may be considerable in proportion to the severity of the disease. This suggests that there is a specific action by the bacterial toxins on the hæmopoietic tissues and the anæmia must be grouped in I A (ii) (a).

**Dysentery**—Any severe dysentery, whether it is caused by bacteria, protozoa or metazoa, may produce an anæmia of the true secondary type that is due to loss of blood. II B. This of course may be acute but it is more frequently subacute or chronic.

In the later stages of these infections the anæmia is due mainly to malabsorption; it is a nutritional dysplasia. I B either sub group (i) (c) or (ii) (c), usually both elements being apparent.

In chronic amœbiasis it has been suggested that the anæmia is due to toxic absorption from the intestinal tract but the evidence for this is not entirely satisfactory, this would place it in group I A (ii).

The anæmia of amœbic hepatitis and liver abscess is often very marked; it is usually normocytic or macrocytic. It can be classified as I B (ii) (d). As the bowel condition improves the blood picture returns slowly to normal but the rate of improvement is accelerated considerably by the administration of liver extract and in some cases this must be considered an essential part of the treatment.

**Other helminthic infections**—*Diphyllobothrium latum* has been reported to cause a normocytic anæmia but the causal relation



malaria they are mostly vegetarians whose protein intake is low and though a particularly low vitamin B complex intake has not always been demonstrated a marked improvement sometimes follows the administration of this vitamin in the form of marmite. However the absence of any appreciable response in the presence of the foetus and the rapid recovery in all moderately severe cases after its removal at term or prematurely suggest the possible action of a pregnancy toxin producing a conditioned deficiency.

Another suggestion is that it is a relative deficiency like that known to occur in the case of iron deficiency in pregnant women but the positions are not parallel because the infantile mortality is very high in TMA suggesting that the foetus also suffers from a deficiency whereas in iron deficiency anaemia the infant takes all the iron it requires and the infantile mortality is low.

Thus to summarize tropical macrocytic anaemia may be (i) a pure dietary deficiency (ii) it may be due to a combination of a poor diet and poor absorption when it is associated with definite bowel syndromes such as sprue or para sprue (iii) it may be due to a combination of a poor diet and repeated malarial infections or (iv) it may be due to the super addition of pregnancy to any of these three causes or to any combination of them.

#### EPIDEMIOLOGY

Since this condition was first described several instances of the pregnancy form have been reported from temperate countries but it is nevertheless essentially a disease of backward tropical countries. It has been shown to be prevalent in India Malaya tropical Africa the West Indies and South America and will probably be found to occur in every tropical country where it is sought.

It occurs mainly in the poor economic classes of the natives or settlers in tropical countries. It may occur at almost any age but it is more common in late adolescence and early adult life and partly because of the association with pregnancy it is more common amongst women than men but it occurs in both sexes. It was more frequently observed in first and second pregnancies.

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#### PATHOLOGY

Our knowledge of the morbid anatomy of this condition is very poor and in the few post mortem examinations that have been performed the associated diseases clouded the picture.

**Blood picture**—The anaemia may be extreme and figures as low as 500 000 red cells per mm and 2 grammes of haemoglobin per 100 c cm of blood are sometimes recorded though in the majority of cases the red cell count will not be much below 2 000 000 per mm. The red cells are macrocytic usually between 100 and 150  $\mu$  the mean corpuscular haemoglobin between 30 and 40  $\gamma\gamma$  and the mean corpuscular haemoglobin concentration between 33 and 37 per cent so that the anaemia is ordinarily a normochromic one. The Price-Jones curve is shifted to the right but tends to retain its normal shape and is not usually a low spread out curve.

terally, and in fact in some cases this seems to tip the balance and cause a complete remission of all symptoms, although in the fully-developed syndrome dietetic treatment also is necessary

### ANÆMIA DUE TO CONGENITAL DEFECTS

*Sickle-celled anæmia* which is confined to negroes, though most of the studies of negroes in anæmia o

sidered tropical, this disease again has been studied mainly in the United States, but nearly all the subjects have been of Mediterranean stock, Italian, Greek, Armenian, or Syrian. However, several cases have been

climate

A short description of the former two conditions will be given here

*Sickle-celled anæmia*—This disease must not be confused with the sickle-cell trait ('sicklæmia'), a condition relatively common amongst individuals of negro stock, occurring in 7.3 per cent of 8453 negroes (Diggs *et al.* 1933), but not necessarily associated with any morbidity, this trait is transmitted hereditarily as a dominant Mendelian characteristic

Sickle-celled anæmia occurs in about 1 in 40 negroes with the sickle-cell trait. Few authentic cases have been reported in persons without some admixture of negro blood. The condition has been diagnosed during the first year of life, most patients come under observation during the first two decades and they seldom survive the third decade

*Pathogenesis*—The sickling phenomenon is associated with 'reduction of the hæmoglobin in the cell, *in vitro*, and apparently also *in vivo*' as for example when a local anoxæmia is caused by constriction of a finger. The shape of the red cell can be restored by oxygenation of the blood. When this sickling occurs in the capillaries of the tissues, an aggregation of the sickled cells apparently results, and stasis and occlusion may follow. Many of the symptoms, for example, the painful crises in the spleen and elsewhere, the heart changes, the secondary pulmonary changes and the ulceration in the legs may be caused by vascular occlusion in different organs and tissues. The compensatory hyperplasia of the bone-marrow will account for the bony changes

The hæmolytic blood picture and the anæmia are caused by the early hæmolysis of the defective sickle cells which in turn leads to the vicious cycle of anoxæmia and further sickling. This anæmia may be classified as III A (1)

*Blood picture*—The red cells are reduced to 2 000 000 or even 1 000 000 per cmm and the corpuscular hæmoglobin the cell will depend entirely on the conditions *in vivo* and *in vitro*, for of local venous congestic show normal or small. The reticulocyte percentage is between 5 and 25 per cent. Normoblasts are constantly present, from 1 to 10 per 100 leucocytes. In a rapidly drawn

sample taken without much previous venous congestion there are usually a few sickle cells present, but if a sealed wet preparation is made the majority of the cells will develop into the sickle or some other bizarre shape within a few hours. The erythrocyte sedimentation rate (ESR) will vary with the degree of oxygenation. A sample taken after a period of local venous congestion will show a very slow ESR, from 1 to 4 mm in one hour, whatever the degree of anemia, but this same sample will usually show a rapid ESR, up to 70 mm or more in one hour, according to the degree of anemia, after oxygenation.

There is a leucocytosis with a large mononuclear increase and a leftward shift in the Arnetz count.

The indirect van den Bergh reaction is strongly positive.

**Symptomatology.**—The patient may suffer from a considerable degree of anemia before any special symptoms develop, and there is usually a history of periodic attacks with symptom free intermissions.

The main symptoms beyond those directly attributable to the anemia namely weakness and breathlessness on exertion, are fever—which may be a low irregular fever or rise to 103° or so, pains in the joints, pains in the abdomen—that may simulate an acute abdominal emergency, enlarged and painful spleen, cardiac dilation, various neurological manifestations, chronic leg ulceration—similar to varicose ulcers and bony deformities—saber tibia, scoliosis and kyphosis.

Roentgenological examination of the bones shows osteoporosis or osteosclerosis, and hair-on-end thickening of the skull. In the retina there is a very marked tortuosity of the vessels.

**Diagnosis.**—Sickling alone is not evidence of sickle-celled anemia, but in sickle celled anemia, if the blood is taken from a vein with an air free syringe (dead space filled with liquid paraffin) and injected into 10 per cent neutral formaldehyde in 0.85 per cent saline 30 to 60 per cent of the cells will be sickled, whereas only an occasional sickled cell will be found in the patient who simply has the sickle-cell tendency.

The following simple method of diagnosis is recommended by Winsor and Burch (1944).

A sphygmomanometer cuff is placed on the arm and inflated sufficiently to stop the venous return for 6 minutes. A sample of 5 ccm of blood is taken into an air free syringe and transferred to a small tube or bottle of the same capacity containing 3 mg of dry ammonium oxalate and 2 mg of dry potassium oxalate. This is immediately corked and rotated gently between the palms to ensure oxalation of the sample. Part of the sample is filled immediately into a Wintrobe's tube which is corked and placed in a vertical position in a suitable rack. The rest of the sample is transferred to a Fienmeyer flask rotated for 15 minutes until the sample is thoroughly oxygenated (it will be apparent from the bright red colour of the blood) and filled into another Wintrobe's tube. In most cases of sickle-celled anemia the difference between the sedimentation rates in the two tubes after an hour will be 60 or 70 mm but a difference of 20 mm which may be observed after as short a time as 15 minutes indicates sickle-celled anemia or at least the sickle-cell trait.

**Treatment.**—This is symptomatic only.

**Prognosis.**—This is always bad, temporary improvements will often occur, but death usually occurs within the first three decades.

**Cooley's anemia.**—This syndrome has recently been separated from the more comprehensive von Jaksch's syndrome. As indicated above it was



first believed to be confined to individuals of Mediterranean stock, but has recently been reported in several Indian children (Napier, Shorten, and Das Gupta 1939) and one Chinese (Foster, 1940).

The most characteristic feature of the disease is the bony changes. In the long bones there is an increase in the medulla with thinning of the compact bone. The general decrease in the density of the medulla leaves the trabeculae standing out, forming a characteristic mosaic pattern in the x-ray picture. In the skull the diploe is thickened to several times its natural thickness with perpendicular striations standing out to give the appearance of hair standing erect on the inner plate of the skull, the outer-plate being invisible.

The blood picture is less characteristic and has features common to other examples of the von Jaksch's syndrome. The degree of anæmia is variable but often considerable. The erythrocytes vary considerably in size from extreme microcytosis to extreme macrocytosis, but the mean corpuscular hemoglobin is low, so that the anæmia is hypochromic. There are frequently 'target' cells present, and many of the red cells are distorted and fragmented. There are many nucleated red cells, mostly normoblasts and always a distinct and sometimes a marked—up to 50,000 per c mm—leucocytosis. The van den Bergh reaction indirect, is usually positive.

The anæmia and the large head are the most striking clinical features.

The steady progress towards a fatal termination is usually uninterrupted. If the symptoms appear in the first year of life death usually occurs within six months, if however they do not appear until later, the child may survive several years. Death is usually due to intercurrent infection.

#### INVESTIGATING ANÆMIA

The causes of anæmia in the tropics are thus numerous and varied. Whenever anæmia is suspected in an individual, or in a group of indi-

viduals, sedimentation rate estimations, the van den Bergh tests, gastric analysis and sternal puncture, should be carried out. In the case of a group these examinations should be done on a random sample of the group with if possible a population. The possible causes of the anæmia, the necessary parasitological and dietary should be reviewed and adequate

With these data and the aid of table XXIX, it should be possible to arrive at a satisfactory conclusion as to the cause of the anæmia. Although the cause even in one individual, is seldom a single factor, the correction of one factor will often reduce the anæmia to negligible proportions.

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## SNAKES AND SNAKE-BITE\*

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*Non specific procedures*

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- (a) Localization of venom  
Tourniquet—Refrigeration

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*Specific treatment*

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PRACTICAL CONSIDERATIONS

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**Introduction**—The practical importance to the ordinary practitioner of his knowledge regarding snakes and snake bites is often neglected by

he will cer-  
tainly be unable  
brought to

Further it is the duty of a practitioner in a tropical country to familiarize himself with the commoner snakes in the locality and thus he cannot hope to do without a knowledge of the essentials of herpetology. This study is important from two points of view—firstly in order to be able to recognize and avoid the bites of poisonous snakes and secondly to they may not be destroyed un-  
are often useful members of the  
frighten away rodents and also

smaller poisonous snakes

CLASSIFICATION

Snakes belong to the class REPTILIA

The class REPTILIA is divided into twelve orders of which eight are extinct. Extant reptiles belong to four orders:

- 1 Crocodilia—crocodiles, alligators and gavials
- 2 Chelonis—tortoises, turtles and terrapins
- 3 Rhynchocephalia—represented by a single living species, the Tuatara or *Sphenodon (Hatteria punctata)* of New Zealand, a lizard like reptile in which the traces of the median eye can still be made out
- 4 Squamata—snakes, lizards, and chameleons

The order Squamata is divided into three sub-orders of which two are still extant, namely

(1) Ophidia (or Serpentes)—snakes

(ii) *Lacertilia*—lizards and chameleons

In the sub order Ophidia (snakes), about twenty-four hundred species have been described, of which over three hundred are sufficiently poisonous to cause fatal effects in man. In India including Burma and Ceylon there are at least 330 species of snakes of which about 70 are poisonous to man (40 terrestrial and 30 marine species), this is the only country in which all the families and sub families are represented.

There are nine families (1) *Typhlopidae*, (2) *Leptotyphlopidae*, (3) *Anilidae*, (4) *Boidae*, (5) *Uropeltidae*, (6) *Xenopeltidae*, (7) *Amblycephalidae*, (8) *Colubridae*, (9) *Viperidae*.

The family *Boidae* includes several of the largest constrictor snakes. In it there are two sub-families, *Pythoninae* and *Boinae*, the former includes *Python repticulatus*, the regal python, the largest snake in the world, which attains a proven length of thirty-three feet, and the latter, *Constrictor constrictor* the boa-constrictor. The *Boidae* are not poisonous but kill their larger prey by coiling around them and crushing them.

All the species of the first seven families are non-poisonous, the last two families include all the poisonous snakes. The *Colubridae* are divided into three groups, three are mildly poisonous, three are mildly poisonous, three are mildly poisonous.

The sub-families of the *Colubridae* and *Viperidae* are sometimes grouped according to the nature and position of their fangs, if these are absent, as in the three non-poisonous sub-families of the *Colubridae*, the snakes are known as 'Aglypha' ( $\gamma\lambda\upsilon\phi\eta$ =a groove), if the fangs are behind the teeth they are known as 'opisthoglypha' ( $\sigma\alpha\iota\sigma\theta\omicron\upsilon$ =behind), if the fangs are developed from the front teeth and are grooved, they are known as 'proteroglypha' ( $\pi\rho\omicron\tau\epsilon\rho\omicron\upsilon$ =before), and if the fangs are hollow tubes (like hypodermic-syringe needles) they are known as 'solenoglypha' ( $\sigma\omega\lambda\eta\upsilon$ =tube).

The families and sub-families of the sub order Ophidia, with their main characteristics and commoner species, are shown in Table XXX (a) and (b).

#### IDENTIFICATION

The identification of the species of a snake is a highly technical procedure that is the domain of the zoologist, or more especially the herpetologist, it takes account of the characteristics of bones and teeth and of the scales as well as the general shape and size of the external characteristics alone. Table XXXI is a provisional identification.

**Poisonous or non-poisonous?**—For practical purposes, it will usually be sufficient to distinguish between the poisonous and the non-poisonous species of snakes.

TAB. XXV (a)

Classification of Snakes		Habitat	
Family	Examples		
1 <i>Typlophidae</i> (non-poisonous) Small worm-like burrowing snakes, uniform small scales, maxilla toothed mandible bare. Tail small, usually as thick as the head and end. Distribution—widespread in tropics. Species—over 100	<i>Typlophs beatus</i> <i>T. diardi</i> <i>T. praxinus</i>	Tropical Asia including India, Tropical Africa, Australia	
2 <i>Leptotyphlopidae</i> or <i>Glaucosidae</i> (non-poisonous) Resembles the preceding family except maxilla bare, mandible toothed tail long. Distribution—cosmopolitan. Species—over 11	<i>Glaucosia blanfordi</i> <i>Leptotyphlops dulcis</i>	India, North America	
3 <i>Anisidae</i> or <i>Eligidae</i> (non-poisonous) Burrowing snakes of variegated colour, usually about 2½ to 3 feet long, claw like spur at the vent representing vestigial remnant of hind limb, ventral shields slightly enlarged. Species—6	<i>Cylindrophis rufus</i> <i>C. maculatus</i> <i>Heteroscyrtus</i>	South-east Asia, Ceylon, Tropical America	
4 <i>Boidae</i> (non-poisonous) Includes several largest constricting serpents, claw like spurs at vent, which are much longer than in the preceding family, very large number of scales on the dorsum of the body. Ventrals are moderately enlarged but do not stretch across abdomen. Sub-family—	<i>Epython molurus</i> (The rock python) <i>P. reticulatus</i> (The royal python) <i>P. apollon</i> <i>Liasis fuscus</i> <i>Constrictor constrictor</i> (Boa constrictor) <i>Funclius murinus</i> (Anaconda) <i>Eryx conicus</i> (so-called two-headed snake) <i>E. johni</i> (so-called two-headed snake)	South-east Asia, India, Burma, Malaya, peninsula etc, Australia, New Guinea, N. Australia, Tropical America, Tropical S. America, India	
(i) <i>Pythoninae</i> Supra-orbital bone present Premaxilla—toothed Species—over 20			
(ii) <i>Boidae</i> Supra-orbital bone present Premaxilla bare Species—about 40			

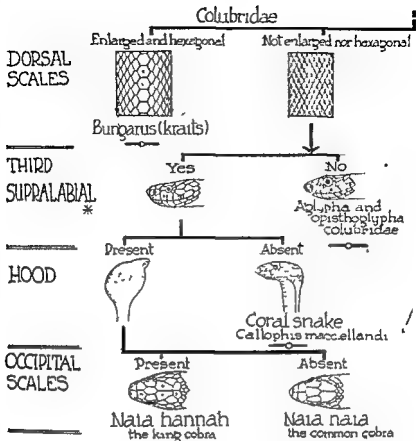
TABLE XXV (b)—(Contd.)

Family	Sub-family	Exemplar	Habitat
8. Colubridæ—(Contd.)			
Opisthoglypha			
Small fangs at the back of the maxilla			
Small poison glands			
	(iv) Homalopsinae (mildly poisonous)	<i>Cerberus rhinoceros</i>	India, S E Asia
	Ventrals slightly enlarged, do not stretch across abdomen	<i>Hyperaspis eurydora</i>	India, S E India
	River and estuarine snakes	<i>H. maculata</i>	Australia
	Tail slightly compressed in many species		
	Species—about 25		
	(v) Elachistodontinae (mildly poisonous)	<i>Elachistodon westernmani</i>	North Bengal
	Lake Dasypeltinae it possesses tooth like projections into the oesophagus to break birds' eggs		
	Species—one		
	(vi) Dipsadomorphinae (mildly poisonous)	<i>Dryophis mycterizans</i> —The green whip snake	S E Asia, India
	A parallel to sub-family Colubrinae, comprising racers, arboreal, and semi aquatic of various size and shape	<i>Chrysopetes ornata</i>	Malaya peninsula
	Species—about 300	<i>Dipsadomorphus trigonatus</i> —The cat snake	South Africa
	(vii) Elapinae (highly poisonous)	<i>D. dendrophilus</i>	Tropical America
	Terrestrial, arboreal or semi-aquatic in habits Tail cylindrical and tapering Ventrals very much enlarged and stretch across abdomen They are among the most deadly of all serpents	<i>Drophioides typus</i> —The boomslang	Tropical Asia including India
	Species—about 180	<i>Pseudoboa clausa</i> —Mussurana	South-eastern Asia
		<i>Naja naja</i> —The common cobra	North Africa
		<i>N. hannah</i> —The king cobra	Africa
		<i>N. haje</i> —The Egyptian cobra or asp.	South Africa
		<i>N. nigricollis</i> —The spitting cobra	India
		<i>N. ferox</i> —The cape cobra	India and South-eastern Asia
		<i>Bungarus candidus</i> —The common krait	Africa
		<i>B. fasciatus</i> —The banded krait	Australia
		<i>Dendraspis angusticeps</i> —Mamba	"
		<i>Pseustes porphyreus</i> —The black snake	"
		<i>Notechis scutatus</i> —The tiger snake	"
		<i>Acanthophis antarcticus</i> —The death adder	"
		<i>Demonia superba</i> —Australian copper head	Eastern India, Southern China, Burma
		<i>Callisaurus macellianus</i> —Coral snake	North America
		<i>Macrurus fulvius</i> —The harlequin snake	
Proteroglypha			
Anterior maxillary teeth grooved (fangs), which are erect and small, connected with highly developed venom glands, venom—neurotoxic			

Family	Sub-family	Examples	Habitat
8 Colubridæ—(Contd.) Proteroglypha	(viii) <i>Hydrophiinae</i> (highly poisonous) Sea snakes. Tail flat ear-shaped. Ventrals either slightly or not enlarged. Nostrils open at the upper surface of snout. Species—over 50	<i>Fekydinus colakadum</i> <i>Dactylophis robustus</i> <i>Hydruis platyrus</i> <i>Pelamysidius platyrus</i>	Indian Ocean, Tropical Pacific Ocean of Asia and Australia. Pacific ocean along Tropical America.
9 Viperidæ (highly poisonous) Locally triangular head distinct and differentiated from a thick body by a narrower neck tail short Pupils vertically elliptical in most cases Ventrals scales very much enlarged, stretching across abdomen Solenoglypha Anterior maxillary teeth are canaliculated (fangs) very large not always erect, can be folded under the palate connected with large venom gland The venom is hemotoxic	(i) <i>Viperinae</i> (highly poisonous) True or pitless vipers. No loreal pit head scales small except in the genus <i>Atheris</i> Distribution—Asia, Africa and Europe. Not found in America or Australia. Species—about 50	<i>Daboia</i> —The Russell's viper <i>Echis carinatus</i> —Phoonna <i>Bais arctatus</i> —The Puff Adder <i>B gabonica</i> —The gaboon viper <i>B nasicornis</i> —The rhinoceros viper <i>Vipera berus</i> —The adder <i>V aspis</i> —The asp <i>Atheris</i> <i>scia</i> —The Fem's viper <i>Crotalus confusus</i> —The rattle snake <i>C adamanteus</i> —Eastern diamond backed rattle snake <i>C atrox</i> —Western diamond rattlesnake <i>C horridus</i> —The banded rattlesnake <i>C terrificus</i> —The dog faced rattlesnake <i>Sistrurus catenatus</i> —The Moosaunga rattlesnake <i>S mitchellii</i> —The pigmy rattlesnake. <i>Atractidion molossus</i> —The copper head <i>A pascuorum</i> —The water moccasin or cotton mouth <i>A bilineatus</i> —The tropical moccasin <i>A lineatus</i> —The Himalayan pit viper <i>A hypsiglena</i> —The Karawala <i>Rhithrops abrax</i> —(B lanceolatus)—The Fer-de-lance <i>B jararaca</i> —The Jararaca <i>B jararacussu</i> —The Jararacussu <i>Lachesis muta</i> —The bushmaster	India, Ceylon, Burma, Thailand N Africa, S.W. Asia, India S.W. Asia, Africa Africa Europe Europe Burma, China North America Central America Himalayas Ceylon, South India South & Central America, W. Indies South America South & Central America India, S.F. Asia East India Eastern India, Burma Southern China
	(ii) <i>Crotalinae</i> (highly poisonous) Rattlesnakes. A loreal pit present between the eye and the nose and rattles on the tail Head snake small in <i>Crotalus</i> head shields in <i>Sistrurus</i> Distribution—America found in Europe Asia, Africa and Australia Species—about 30		
	(iii) <i>Lacertinae</i> (highly poisonous) A loreal pit but no rattles small head scales except the genus <i>Atractidion</i> Distribution—America and Asia Species—about 70		







**Key** Where the name is printed in Large type it indicates that the species is a poisonous one, or if it is the name of a family subfamily or genus that all or many of its members are poisonous

For example, all **HYDROPHINAE** or sea snakes are poisonous, so are **Crotalinae**, **Lachninae** and **Viperinae**. **Colubridae** contain both poisonous and non-poisonous species

On the other hand the **Typhlopidae**, etc are non-poisonous, so are the **Amblycephalidae**. Of the **Colubridae**, **Bungarus**, **Naja hannah** and **Naja naja** are very poisonous. **Coral snakes** are poisonous but not so highly poisonous and the **aglypha** and **opisthophlypha Colubridae** are non-poisonous

(If this diagram is copied for class purposes the poisonous snakes should be printed in red ink)

\* The third supralabial scale touches both the eye and the nasal scale in the poisonous Colubridae

If simplex examin		
<i>Aglyphous</i>	two rows of teeth on either side of the maxilla and no fangs	non-poisonous
<i>Opisthoglyphous</i>	two rows of teeth with one pair of grooved fangs at posterior end of outer row	mildly poisonous
<i>Proteroglyphous</i>		
<i>Solenoglyphous</i>	one row of teeth with a pair of long tubular movable fangs and one or more pairs of accessory fangs	poisonous

TABLE XXXI

*Data required for identifying the species of a snake from its external characters*

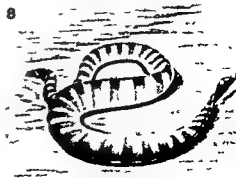
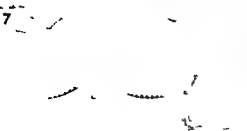
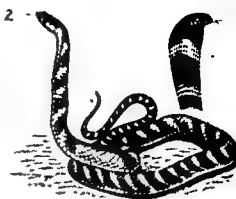
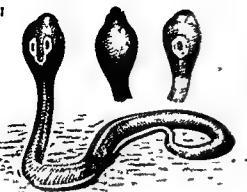
- 1) SIZE
  - (a) Length including the tail,
  - (b) Length of the tail only
- 2) SHAPE OR FORM
  - (a) Tail—whether flat or cylindrical, tapering slender or stumpy, bevelled rounded or pointed, rattles present or not
  - (b) Body—whether stout, moderate sized or slender
  - (c) Head—whether distinct from the neck or not, broad or narrow, high or flat
    - (i) Snout—pointed or obtuse
    - (ii) Snout
    - (iii)
    - (iv) It or
    - (v)
  - (vi) Ioreal pit between eyes and nostril—present or not
- 3) COLORATION
 

Ground colour of the dorsum and venter, any colour pattern such as longitudinal and transverse markings stripes or streaks spot, rings or other markings. Markings on the head and tail
- 4) ARRANGEMENT OF SCALES OR EPIDERMIS
  - (a) Body and tail
    - (i) Ventrals—whether broad moderate sized or narrow, or if broad then number
    - entire
    - in the mid
    - thei distre or
    - or keeled or
    - hexagonal or
  - (b) Head
    - (i) Whether shields or scales if shields—then pattern shape and size
    - (ii) Supra labials—their number and pattern especially the relation of the 3rd supra labial in the family *Colubridae*
    - (iii) Infra labials—their number and pattern
    - (iv) Sublinguals—size and shape, whether the mental groove is present
- 5) ARRANGEMENT AND CHARACTER OF TEETH
  - (i) Whether both maxillae and mandibles are toothed
  - (ii) How many rows of teeth on the upper jaw
  - (iii) Premaxilla toothed or not
  - (iv) Fangs present or not, if present—whether anterior or posterior grooved or hollow tubes

\* Great care should be exercised in examining recently killed snakes as muscular spasm may occur and many people have been bitten by a dead snake

# COMMON POISONOUS SNAKES OF INDIA

- 1 Common cobra *Naja naja*. A snake. It well mark'd hood the mark on the back of the hood differ in different colour variat. It—buccellae middle—ovalate right—monocellate. Colour of the body black brown buff or wheat-coloured rarely white. Abdomen—white or yellow. Length—1 to 6 feet or more. Girth—moderate. *Lepidos* ventral stretching across abdomen. Scales on the head the supra labial touches the eye and the nasal scale subaudals—double.
- 2 King cobra *Naja hannah*. Hood—not so well marked. Length—usually 8 to 12 feet. Head small. Head and tail and the nasal scale subaudals—entirely double.
- 3 Common krait *Bungarus candus*. Length—all 3 or 4 feet. Steel like in colour. It white line across back. *Lepidos* entire is stretching across abdomen. Scales on head vertebrals enlarged and hexagonal subcaudal—entire.
- 4 Banded krait *Bungarus fasciatus*. A big stout snake grows to about 5 to 6 feet or even 7 feet long. Body white or blue line. Tail—rather blunt. Very sluggish in habit. *Lepidos*—entire 3.
- 5 Russell's viper *Daboia russellii*. Length—3 to 4 feet. Snake body triangular and flat head large eyes with vertically elliptical pupils. Nostrils short. Abdomen—oval. Caudal—entire.
- 6 Saw-scaled viper or Phoxiphan *Echiscara*. Small snake. It has 12 feet. Head—triangular with distinct when black or brown. Colour of the body—brown black or sandy with a greenish yellow. It is triangular. Abdomen—oval. Scales on head subcaudal—entire.
- 7 A sea snake *Flydrina alabaden*. A robust snake. It is flat or raptorial like all other. It is brown. Nostrils—entirely on the head. Colour—black. Length—entirely on the head.



Snakes can also be identified with a fair degree of certainty by distinguishing certain external characteristics, and using the scheme 'Identification of Poisonous Snakes'.

It is important to remember that colour is seldom of use in distinguishing characteristic, the colour of most species is variable to a greater or lesser degree. However, plate D, will give some idea of the uses of some of the more common Indian poisonous snakes.

## SNAKE-BITE

**Epidemiology.**—The geographical distribution of snake bite is usually dependent on the geographical distribution of the dangerous species of venomous snakes, this can be seen from Table XXXI. India, the Indies, tropical Africa and tropical America are the fields richest in snakes and India with at least 70 species of poisonous snakes heads the list.

On the other hand, there are many islands that are free from terrestrial poisonous snakes, e.g. Iceland, Ireland, New Zealand, Madagascar, Hawaii and many islands in the South Pacific and several in the West Indies.

In Europe there are few poisonous snakes, the most common are the adder (*Vipera berus*) and the asp (*I. aspis*).

In Australia, the commonest causes of snake bite death are the death adder (*Acanthophis antarcticus*), the tiger snake (*Notechis scutatus*) and the black snake (*Pseudechis porphyriacus*).

In Africa, the commonest deadly snakes are the mamba (*Dendroaspis angusticeps*), the spitting cobra (*Naja nigricollis*), the puff adder (*Bitis arietans*), the rhinoceros viper (*B. nasicornis*), the asp (*Naja haje*) and the Cape cobra (*Naja flava*).

In North America poisonous snakes are relatively common in the mountainous and marshy districts. The best known are the rattlesnakes, the diamond backed rattlers (*Crotalus atrox* and *adamanteus*), the banded rattlesnake (*C. horridus*) and the massasauga (*Sistrurus catenatus*), the rattlesnake pit vipers, the water moccasin or cotton-mouth (*Ictalodon punctatus*) and the copperhead (*A. mohavensis*) and the harlequin (coral) snake (*Victorinus fulvius*).

In South and Central America, the most feared snakes are the bush-master (*Lachesis muta*), the fer-de-lance (*Bothrops atrox*) and the jararaca (*Bothrops jararaca*), but there are many other species.

In India, the cobras, the kraits, the Russell's viper and the echis viper are the snakes mainly responsible for the high mortality.

In countries where poisonous snakes are abundant death from snake-bite constitutes not an unimportant cause of mortality. Between 20,000 and 50,000 deaths from snake-bite are reported annually in British India, though snake-bite is sometimes a convenient euphemism for death by other instances death from snake-bite will escape registration, so that on the whole the figure probably represents something near the truth. On the other hand, in Australia between 1910 and 1926 the annual deaths from snake-bite numbered less than 15. For the whole world the annual deaths from snake-bite are usually placed between 5,000 and 10,000.

Few snakes are aggressive as far as man and other large mammals are concerned, and the majority bite only when attacked, frightened, or accidentally injured. The persons most affected therefore are the bare-footed villagers walking along a jungle path at night who may accidentally tread on a snake. The snake may be stepped on in the house to escape unfavourable circumstances—and it is not uncommon for a woman to place her foot frequently on a snake.

hand into a receptacle in a dark corner

in and outside their huts, and the stage of cases in children, the toxic between the amount of venom injected and the body weight of the subject

### ANATOMY AND TOXICOLOGY

**Poison apparatus.**—This consists of a pair of poison glands connected by ducts to the grooved or canaliculated fangs on the maxillæ. The poison glands are modified supra-labial glands, analogous to the parotid glands of the mammals. They occupy an intermuscular space in the temporal regions below and behind the orbit, on either side of the upper jaw (maxillæ).

The glands are enveloped by a fibrous capsule to which are partly attached the fibres of the masseter muscles and are surrounded by a group of muscles, consisting of the anterior, middle and posterior temporal, and the digastric. During the act of striking, these muscles are involuntarily contracted and the glands are violently squeezed, so that the venom is driven along the duct to the grooved or canaliculated fangs and thence to the tissues of the victim, even if the snake misses its victim, venom will sometimes be ejected. The venom of the spitting cobra, *Naja nigricollis*, can be ejected a distance of 6 to 8 feet and it will cause temporary blindness if it comes in contact with the eyes. In other species, especially the opisthoglyphæ, the actual pressure of the bite appears to be necessary to eject the venom.

In the proteroglyphæ and solenoglyphæ, the fangs, which are situated anteriorly on the maxillæ, differ one from the other in their structure, size and shape. In the proteroglyphæ (*Colubridæ*), the fangs, though slightly movable, are erect and small, the groove, which runs anteriorly lengthwise from the tip, is covered by a

when these muscles are relaxed, the fangs lie inside a sheath of mucous membrane (vagina dentis), but when the muscles are contracted for the strike or bite the fangs come forward automatically and project at a right angle from the

when the main fangs are broken

**The venom.**—Physical nature.—It is a colourless or golden-yellow





hæmorrhagin represents about 70 to 75 per cent of the total toxicity, the cytolytins, thrombase and cardiac toxin represent about 20 to 25 per cent and the proteolytic enzyme the balance. But there are exceptions to this rule, as in *Crotalus terrificus* a viper, the venom is strongly neurotoxic.

**Minimal lethal doses of different venoms for man**—Acton and Knowles (1921) estimated the minimal lethal dose (MLD) of cobra venom for man to be 15 mgm by a study of fatal cases of cobra bite given in the literature in which no treatment or valueless treatment had been administered. The MLD for the venoms of other Indian species of poisonous snakes was also calculated by them on the assumption that the relative toxicities of different venoms for the monkey hold good for man.

The data in the following table were taken from their papers and from other sources.

TABLE XXII

Snake	Approximate dose given at bite mgm	Estimated fatal dose for man mgm
<i>Naja naja</i>	211.3	150
<i>Naja hannah</i>	100.0	120
<i>Bungarus candidus</i>	5.4	10
<i>B. fasciatus</i>	42.9	100
<i>Daboia russellii</i>	72.0	42.0
<i>Echis carinatus</i>	12.3	50
<i>Trimeresurus gramineus</i>	14.1	100.0
<i>Apisirodon makasen</i>	45-60	} approx imately 250
<i>A. pectorus</i>	90-150	
<i>Crotalus horridus</i>	60-90	
<i>C. adamanteus</i>	240-450	
<i>Bothrops atrox</i>	80-160	
<i>Lachesis muta</i>	300-500	}
<i>Dendroaspis angusticeps</i> (Mamba)	50-80	

### SYMPTOMATOLOGY

As the toxic principles in colubrine and viperine venoms differ, the symptoms produced in the victim after the bites of the snakes of these two families are also different and they are therefore considered separately.

**Symptoms after colubrine (cobra) bite**—Local. Immediately after the bite there is a burning sensation at the site which passes off in a few minutes, this is followed by loss of sensation and paralysis of the area around the site, where a moderate amount of œdema supervenes. There is oozing of blood from the fang punctures as the blood does not coagulate on account of the action of anticoagulin.

**General**—The neurotoxins act on the motor end plates of muscles, on the respiratory centre and on the centres of the 9th, 10th, 11th and 12th nerves. The following is the usual sequence of symptoms—drooping of the eyelids, unsteady gait, incoordination of speech, slight difficulty in respiration. Paralysis starts from the lower extremities except for the local paralysis and proceeds upwards. With the complete paralysis of all the voluntary muscles there is drooping of the head and difficulty in deglutition. Apyrexial symptoms supervene, breathing becomes shallow and rapid, and the face becomes cyanotic. There is profuse salivation. Later convulsions start and there is vomiting and involuntary passage of urine and faeces. Finally, the victim dies of respiratory failure. The pulse is little affected except as a result of primary shock which is

mainly due to fright. The heart continues to beat after the respiration has failed. Consciousness is retained almost to the last. Death usually takes place in untreated cases in from one to six hours.

The symptoms after krait bite are similar to those of cobra bite with an additional symptom of violent abdominal pain which is associated with hemorrhages in the stomach and the intestines.

Authentic cases of sea snake bite are rare. The symptoms caused by their bite are similar to those after cobra bite.

**Symptoms after viperine bite (Russell's viper) —Local** Immediately after the bite there is an intense burning pain which persists along with the incessant oozing of blood from fang punctures. There is also marked oedema and redness of the area and later ecchymoses around the puncture. There is no loss of sensation or paralysis of the bitten part.

**General** The hemorrhagin destroys the endothelial cells of the finer capillaries and blood escapes through them. In consequence there is evidence of external as well as internal hemorrhages. There may be epistaxis, hematuria, hemoptysis, hamatemesis, melena, sub-conjunctival

supervenes in fatal case of viper bite. Death usually takes place in two to six days.

The above symptoms are produced if a moderate quantity of venom is injected. If on the other hand a large amount is injected with the bite death occurs in a few hours as the result of acute cardiac and vasomotor failure or if by any chance the venom is introduced directly into a vein death follows within a few minutes as the result of intravascular and intracardiac coagulation but this occurrence is very rare in human beings. Whereas death after Russell's viper bite is usually due to vasomotor paralysis or to septic absorption from the extensive local gangrene in the case of *Echis* bite death is usually due to multiple hemorrhages.

**The effect of the bite of the rattlesnake** —The effect of the bite of the rattlesnake genus *Crotalus* is similar to that of the viper. There is much pain, local swelling and hemorrhagic reaction. The hemorrhagic mottling and swelling tend to spread up the limb from the site of the bite. Later general symptoms of viperine poisoning develop. The exception to this rule is the bite of dog faced rattle snake (*Crotalus terrificus*) whose venom is strongly neurotoxic and causes little local reaction but later the vision and respiratory centres are affected.

### DIAGNOSIS

The first important point to decide is whether the patient has been bitten at all. If the patient is on poisonous substances, the snake will seldom be seen. Identification possible. On rare occasions the offender is caught and killed then it will usually be possible to decide on its identity (see p 846). Diagnosis will

therefore often depend largely on the local examination for marks and on the signs and symptoms presented by the patient. But diagnosis is not easy, one cannot afford to await the development of typical symptoms or it will be too late to take any action.

The part where the bite is supposed to have occurred should be examined carefully for the teeth and/or fang marks. The harmless aglyphous and the relatively harmless opisthoglyphous snakes may leave the marks of two double rows of teeth, the posterior fang of the snakes of the latter group seldom coming into action when biting man, whereas the proteroglyphs

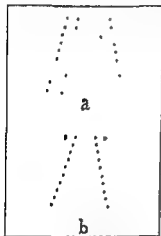


Figure 195 Showing upper-jaw fang marks of

- (a) Aglyphous (non-poisonous) snake
- (b) Proteroglyphous (poisonous) snake

glypha often leave only a pair of bleeding fang marks, as they 'strike' rather than 'bite'. The larger the snake the greater the distance between the fang marks.

Before considering the diagnostic points in the symptomatology of poisonous snake-bite, it will be as well to review the symptoms that are likely to occur after the bite of a non-poisonous snake.

**Non-poisonous snake-bite.**—Fear of snake-bite is so highly developed in the human race that many people suffer from a severe degree of primary shock even after a bite by a non-poisonous snake. In so-called strong-nerved—that is unimaginative—individuals, one might be able to discount the effects of fear, but it is no easy matter to gauge a person's

snake. In a person who is familiar with the symptoms of snake bite, all the usual signs and symptoms as a result of a bite by a non-poisonous snake are likely to be absent. In such a case, the result may be simulated by a hysterical patient.

slight and fang marks will be absent. In all cases, there will be no bleeding from the bite, nor paralysis, but these may be simulated by a hysterical patient.

**Differentiation between colubrine and viperine poisoning.**—This also is difficult in the early stages when the differentiation may be of any value. In colubrine poisoning, local pain passes fairly rapidly and is replaced by local anaesthesia, local paralysis develops, and there is some local oedema. In viperine poisoning, local pain is marked and persistent; there is a more intense local reaction which may include echymosis around the puncture,

and there will be no local paralysis. In the later stages, more marked differences in the general symptoms appear (*vide supra*). Shortly, the predominant symptoms in the former are paralytic, and in the latter hæmorrhagic.

### PROGNOSIS

This is dependent on a large number of factors several of which are unappraisable, and it must therefore be very guarded. (It is however essential that the patient himself must be reassured for his own sake.)

The factors concerned are

(a) the species of the snake and the individual variation in the toxicity of its venom, (b) the amount of venom injected (c) the site of the bite, (d) the body-weight of the victim (e) the immediate measures adopted, and (f) the facilities available for treatment.

(a) If the snake is not identified, this factor can only be gauged in general terms, for example the snakes of Europe, Australia, and temperate countries generally are much less poisonous than those of India and other tropical countries.

(b) The amount of venom injected is dependent on the efficacy of the bite which will to some extent depend on (c) the part bitten, a bite on a small member, such as a finger or toe, or even hand or foot is likely to be more effective as, for mechanical reasons the poisoning mechanism can come into full play, on the other hand, in such a position it will be easier to give effective local treatment.

(d) The body weight is important, as the effect of a given amount of poison will be in inverse ratio to the body-weight, therefore the larger the individual the better are his chances of recovery.

(e) The prompter the application of the ligatures and other immediate measures, the better the prognosis.

(f) Finally, to be of any use specific or polyvalent serum must not only be immediately available, but available in sufficient amount.

### TREATMENT

**Introduction**—More fables have grown up around the treatment of snake bite than around any other procedure in medical practice. Many millions of inhabitants of eastern countries are firm believers in amulets, snake stones, potions with a most diverse range of ingredients—from plant juices to powdered gall stones—and/or prayers and incantations as in fallible cures for snake-bite. This credulity is not confined to the uneducated classes nor even to the inhabitants of eastern countries, for there is a widespread belief amongst the laity of western countries—a belief that is even accorded semi-official recognition in countries where 'prohibition' is in force—that the drinking of a bottle of whiskey is the best treatment.

unity

There is no specific treatment for snake bite other than the appropriate antivenom serum, although there are many non specific procedures,

that must be considered as adjuvants when antivenene is available and substitutes when it is not

It will be suitable first to consider shortly these non-specific procedures, then the specific treatment, and finally the practical aspects of the treatment of snake-bite in various circumstances

### Non-specific Procedures

(a) **Localization of the venom**—(1) **Tourniquet**.—The application of some form of tourniquet, either a tightly applied one to prevent arterial flow, or a lightly applied one to cause venous congestion and control lymph return, appears to be the common-sense procedure, but nevertheless it is not a measure that is universally recommended. The main case against the tourniquet is that no tourniquet will prevent poison spreading through the tissues and an arterial tourniquet at least will often do considerable and unnecessary local damage. On the other hand, most practical workers consider that a lightly-applied tourniquet is always beneficial and some recommend an arterial tourniquet as well. The writers believe that combined with other measures at least a light ligature should be applied, and one of us (S K G) has seen marked benefit from an arterial ligature in preventing the neurotoxin reaching the central nervous system in colubrine bites

(2) **Refrigeration**.—There is little practical support for this theoretically plausible procedure, but it is sometimes worth practising if only for its psychological effect

(b) **Elimination of venom at the site**—(1) **Multiple incisions** should be made with aseptic precautions and if possible under local anaesthesia a large deep ( $\frac{1}{4}$  to  $\frac{1}{2}$  inch according to the depth of the bite) crucial incision through the fang marks and a series of small ( $\frac{1}{4}$  inch by  $\frac{1}{4}$  inch) incisions around the edge of the advancing swelling, blood vessels must be avoided and, if cut, tied

(2) **Suction** may be effected by means of Bier's suction tubes, a breast that suggested by Jackson a wound should be looked be combined with ligature and saline irrigation, and continued for a long time. Although much of the toxin is absorbed by the local tissues, a considerable amount can be extracted by this means, as experience has shown that the extracted fluid is very toxic

(3) The objects of **excision** and **amputation** are the same, namely, the removal of the tissues in which the toxin is fixed. The choice of procedure will depend on the site of the bite, and amputation should only be

(c) **Neutralization of the venom in situ**.—Local infiltration with calcium hypochlorite, potassium permanganate, gold chloride or other substances, some of a secret nature, has been advocated in the past and is still considered by some workers to be a valuable procedure. However, the present trend of opinion is against any local injection, except with anti-venene. The latter, if available, should always be used, at least in the case

of viper bite and as much as they will take should be infiltrated into the tissues around the bite

- (d) **Treatment of general symptoms**—(i) **Primary shock**—The patient should be placed head slightly lower than his feet, reassured and calmed. Caffeine  $\frac{1}{4}$  gram, if there is severe pain, is given. It is obvious that the bite was a non-poisonous one in such a case given in moderate amounts it will help to combat primary shock from fear.

(ii) **Secondary shock and collapse**—Hæmorrhages and vasomotor failure may lead to collapse which should be combated by the usual procedures including plasma or serum transfusions of at least two pints and pituitrin and adrenalin. In the absence of plasma whole blood may be used. Chopra and Chowhan (1939) strongly advocate veritol (15-30 mg intramuscularly or 40-80 mg by mouth).

(iii) **Respiratory paralysis**—caused by the neurotoxins may occur. Respiratory stimulants such as coramine and cardiazol by the parenteral route may help to alleviate respiratory embarrassment but in some cases artificial respiration and oxygen may have to be maintained for several hours.

(iv) **Respiratory paralysis**, caused by the neurotoxins may occur. Respiratory stimulants such as coramine and cardiazol by the parenteral route may help to alleviate respiratory embarrassment but in some cases artificial respiration and oxygen may have to be maintained for several hours.

(e) **Treatment of complications and sequelæ**—(i) **Sepsis**—Septic absorption from the site after viperine bite is not uncommon. Early administration of drugs of the sulphonamide group prevent this complication. Some authorities advocate the routine use of antitetanic serum in prophylactic doses.

(ii) **Gangrene**—It frequently occurs after viperine bite and is due to the action of thrombase. Early administration of antivenene early release of the ligatures and when the general symptoms appear to be well controlled vigorous local treatment with frequent hot fomentations will usually prevent gangrene but once it supervenes amputation is the only remedy.

(iii) **Other complications and sequelæ**—*Hæmopericardium hæmothorax hæmarthrosis pyæmia* and *nephritis* are some of the sequelæ of viperine bite each of these requires its own line of treatment.

#### SPECIFIC TREATMENT

**Antivenene**—The only specific treatment against poisonous snake bites is the early administration by the intravenous route of antivenom serum so called antivenene. As the venoms of different species of snakes differ in their toxic principles different antibodies are produced in the immunized animal (horse) and the antiserum produced against the venom of a particular species is effective against that venom alone or against the venom of closely related species. For example in India antivenene either against cobra venom or Russell's viper venom (the two commonest poisonous species which are responsible for the majority of the 20,000 or more annual snake bite deaths) will not protect the victim bitten by the other species. To surmount this difficulty polyvalent sera which are effective against more than one common local species have been prepared by serum

that must be considered as adjuvants when antivenene is available and as substitutes when it is not

It will be suitable first to consider shortly these non specific procedures, then the specific treatment, and finally the practical aspects of the treatment of snake bite in various circumstances

### Non-specific Procedures

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and, if cut tied

(ii) pump, or (1929)

upon as a 'first-aid' measure. Suction must be combined with ligature and saline irrigation, and continued for a long time. Although much of the toxin is absorbed by the local tissues a considerable amount can be extracted by this means, as experience has shown that the extracted fluid is very toxic

(iii) The objects of excision and amputation are the same namely, the removal of the tissues in which the toxin is fixed. The choice of procedure will depend on the site of the bite and amputation should only be considered in the case of bites on the toes or fingers. These measures should only be undertaken when the limb has been effectively ligatured continuously since the bite, or when it is possible to excise the site or amputate the limb immediately after the bite

(c) **Neutralization of the venom in situ** — Local infiltration with calcium hypochlorite, potassium permanganate, gold chloride or other substances, some of a secret nature, has been advocated in the past and is still considered by some workers to be a valuable procedure. However the present trend of opinion is against any local injection except with antivenene. The latter, if available should always be used at least in the case

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- (d) **Treatment of general symptoms**—(i) **Primary shock**.—The patient lies on his back, with his head lower than his feet and calmed by morphine. If there is severe pain at the bite a non-poisonous one, in such a case, given in moderate amounts, it will help to combat primary shock from fear

(ii) **Secondary shock and collapse**—Hæmorrhages and vasomotor failure may lead to collapse which should be combated by the usual procedures, including plasma or serum transfusions of at least two pints, and pituitrin and adrenalin. In the absence of plasma, whole blood may be used. Chopra and Chowhan (1939) strongly advocate veritol (15-30 mg intramuscularly or 40-80 mg by mouth)

(iii) **Hæmorrhages**—For the multiple hæmorrhages after viperine bite, injections of calcium chloride or gluconate, congo red solution, vitamin C, vitamin K and hæmostatic serum have all been advocated and each appears to have been of value in certain cases

(iv) **Respiratory paralysis**, caused by the neurotoxins, may occur. Respiratory stimulants such as coramine, and cardiazol by the parenteral route may help to alleviate respiratory embarrassment but in some cases artificial respiration and oxygen may have to be maintained for several hours

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institutes of different countries \* Heterologous serum is sometimes used but there is little evidence that it is of any real value

**Dosage.**—The points to be considered in calculating antivenene dosage are —

(a) The amount of venom inoculated, this is an unknown quantity, but the average quantity injected by a snake of the particular species is usually known (see table XXXII, p 850), and some idea of the efficacy of the bite may be obtained from the site and the circumstances of the bite

(b) The toxic activity of the venom of the individual snake, this is always an unknown quantity, but is likely to vary from country to country and the venom is usually more toxic in tropical countries

(c) The neutralizing capacity of the antivenene, for example, whether it is concentrated or not; 1 c cm of polyvalent antivenene (Kasauli) given intravenously will neutralize 0.4 mgm of dried cobra venom or 0.9 mgm of daboia venom

(d) The time that has elapsed after the bite

(e) The route of administration, the intravenous route is three to four times more effective than the intramuscular or subcutaneous

It will be seen from the above and from table XXXII on p 850 that the amount of concentrated polyvalent antivenene, for intravenous in-

should be remembered that such large doses of horse serum by the in-

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\* In India, the Central Research Institute, Kasauli (Punjab) prepares and issues concentrated antivenene which is effective concentrated four times 10 c cm of unconcentrated of the Institute at a

cost of about four rupees per ampoule

Polyvalent high titre antivenene against two or more different local species are being produced by —

(a) Butantan Institute in Sao Paulo, Brazil South America prepares four polyvalent antivenenes against (i) rattlesnakes (ii) Bothrops (iii) rattlesnakes and Bothrops, and (iv) coral snakes

venene against the *labou*, *see* *et* *ed* *on* *—*

(e) Public Health Department of New South Wales, Australia prepares an

prepare a 'nearctic cratolidae' (spers) and a Bothrops anti-

1 c cm of serum which have  
It is probable that the  
to a powder will be applied  
essuy of keeping them in a

travenous route may cause severe anaphylactic symptoms in susceptible individuals

**Precautions**—In the case of persons giving a history of allergy, such as asthma or hay fever, or of previous injection of horse serum a test for sensitiveness to the proteins of horse serum must be made by giving intradermally 0.1 c cm of a 1-in-10 dilution of horse serum. If no skin reaction

the patient before giving the main dose

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occur, the injection should at once be stopped and 1/50th gr of atropin and 0.5 c cm of a 1 in 1 000 solution of adrenalin chloride should be administered hypodermically

We have usually adopted the practice of giving 50 c cm of concentrated antivenene intravenously diluted with the same quantity of 25 per cent glucose solution to start with and then the balance of the dose slowly in a pint of 5 per cent glucose in normal saline. No ill-effects were noticed in any of the patients.

After the requisite quantity of antivenene has been given the ligatures may be removed.

#### PRACTICAL CONSIDERATIONS

When a man is bitten by a snake the first problems facing the practitioner are: (1) Was the patient actually bitten at all? (2) Was the snake a poisonous one? (3) Was the dose of antivenene a dangerous one? (4) He then has to decide how far he is justified in carrying out possibly mutilating procedures on the chance that the snake may have been a poisonous one and that the dose may have been one that would ordinarily prove fatal.

If the snake is captured or killed and is not too badly mutilated it may be used for tooth and/or for the surrounding

Prompt action is necessary. It must be weighed on the evidence available. It is naturally somewhat difficult to decide what treatment is to be given. If the snake is poisonous it would be wrong to withhold antivenene on the grounds that it would hesitate to take such drastic procedures as amputating a limb or even making extensive incisions which might damage important structures and would usually be a potential source of sepsis unless the suspicion were well founded.

It will be as well now to consider the case of snake bite as an emergency in four different sets of circumstances:

A In the jungle or bush where no medical equipment is available and first aid has to be applied

B In the isolated village dispensary where no antivenene is obtainable

C In an out-station hospital where, although there is no antivenene at hand this will be obtainable within a few hours

D In a well-equipped hospital where antivenene is available in sufficient quantity

A In the jungle or bush where no medical equipment is available, and 'first aid' has to be applied—A ligature must be placed immediately

suction should be applied over the punctures and, if a sharp and reasonably clean knife is available, a crucial incision may be made into the fang marks to facilitate effective suction, but it is doubtful if any further cutting procedures should be undertaken in these circumstances. The patient must be reassured as far as possible and, when they are available, given hot coffee or tea to drink and  $\frac{1}{4}$  grain of morphia subcutaneously. He must then be removed to the nearest place where further treatment can be given.

Wherever possible the snake should be killed, without damaging the head unduly, and identified or preserved for identification.

Do not give alcohol if it is thought that the bite was by a poisonous snake, as it is definitely detrimental.

B In the isolated village dispensary where no antivenene is obtainable—This is the situation that probably nine times out of ten faces the medical man who has to treat snake bite in tropical countries. A firm ligature sufficient to stop the lymph flow and the venous return should be

applied (vide supra). The patient should be kept closely regarding the incident of the snake having been a poisonous one. This will be facilitated if the snake was killed and brought with the patient. If the decision is in favour of an effective bite by a poisonous snake, then under a local or a general anæsthetic a series of incisions should be made under strict antiseptic conditions, one deep crucial incision immediately over the bite, a number of shallower ( $\frac{1}{4}$  inch) crucial incisions in a circle around the bite at the edge of the swelling and, if the swollen area is a wide one several incisions should be made within this

and any symptoms that have developed

at the moment

Other treatment for secondary shock and other general symptoms, and for the various complications that may arise will naturally be given (vide supra).



## RABIES

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**Definition**—Rabies or hydrophobia is a zootic disease which is potentially world wide in its distribution but has been excluded from certain countries and entirely banished from others it is however always a serious problem in the tropics. It is caused by a filtrable virus which is transmitted to man by the bite of carnivores usually canines. The virus spreads along the nerves and the symptoms are mainly of a nervous nature excitation and/or depression and later paralysis. When the symptoms are established the disease is invariably fatal.

### EPIDEMIOLOGY

One of the reasons for the relatively heavy incidence of rabies in the tropics is the presence of innumerable stray dogs and of other actual and potential reservoirs of infection for example jackals foxes and mongoose in India and vampire bats in Brazil Trinidad and Jamaica. Another cause is general administrative and sanitary backwardness in these countries.

The disease is very widespread in India and in the Pasteur Institute in Calcutta which is only one of several such institutes in the country as many as 10 000 persons undergo anti rabic treatment annually. It is also very prevalent in Africa and South and Central America.

The disease has apparently never been introduced into Australia this is the result of rigid quarantine rules aided possibly by the absence of any

potential wild reservoirs of infection. It was banished from Great Britain by rigidly enforced muzzling orders of half a century ago as well as by adoption of a six months quarantine period for imported dogs but was temporarily reintroduced after the First World War apparently by returning soldiers' dogs which evaded the quarantine regulations. In the United States where the control problem is admittedly a complex one account of its many miles of land frontier between fifty and sixty deaths from rabies occur each year.

There is a popular superstition that the disease is confined to certain seasons of the year especially the late summer days. There is no statistical support for this belief.

### ÆTIOLOGY

The causal organism is a medium sized filtrable virus about 125 microns in diameter. For infection to occur the virus must reach nervous tissue, it cannot therefore be transmitted through the unbroken skin or mucous membrane.

By repeated sub passage of the virus directly on to the brain of a series of rabbits or sheep it is possible to change an ordinary street virus with its long and inconstant incubation period into a virus with a fixed incubation period of three to six days. After attenuation—by one of several recognized methods—this fixed virus introduced subcutaneously into man is usually innocuous but retains its antigenic properties.

Most animals are susceptible to infection but not all are capable of transmitting the disease. True of the large herbivores. As far as man is concerned, dogs and cats are the only important sources. Dogs may act as regional reservoirs. In 1941 out of 7877 cases

of rabies 6648 were in dogs. The dog may have the virus in its saliva 3 to 4 days before symptoms of the disease appear and it remains infectious until its death usually occurring within six days of the onset of symptoms.

### PATHOGENESIS

The virus spreads up the nerve trunks until it reaches the cord from where it enters the brain.

The most characteristic specific changes are produced in the pyramidal cells of the hippocampus major where the specific Negri bodies are most readily found though they are often present in other nerve cells in the brain. Negri bodies are acidophilic bodies observed in the cytoplasm of the nerve ganglion cell, they vary considerably in size and shape usually being 3 to 10 microns in diameter and round or oval in shape and granular in appearance. Negri bodies are not parasitic structures but result from the reaction of the cell to the virus and are comparable to the inclusion bodies that are seen in various parenchyma cells in other viral infections.

## SYMPTOMATOLOGY

The incubation period is from two weeks to six months, this is influenced by several factors, including the site of the bite (*vide supra*). The onset is usually preceded by a day or so of malaise, headache, insomnia, irritability, and slight fever, or the onset may be sudden, with the development of periods of restlessness, anxiety and hyperexcitability. Breathing becomes rapid and 'air-hunger' may develop. These periods of excitement alternate with periods of calm, but the former tend to become longer and soon are accompanied by actual spasms of muscle groups, such as those of deglutition. These spasms are precipitated when the patient attempts to drink, and in his thirsty state even the sight or thought of water may cause the spasmodic retraction of the head in a series of jerks. Spasms are also precipitated by the sight of food.

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and the mouth is often filled with a ropey and frothy mucus. There is often a low fever.

Eventually, the patient sinks into a paralysed and weak state and death follows, or this may occur suddenly during one of the spasms, within 2 to 3 days of the onset of symptoms.

Other types have been described, including a form in which paralysis develops from the onset and simulates acute ascending myelitis.

## DIAGNOSIS

The combination of the history and clinical picture are usually sufficient to make a diagnosis certain, but hysteria, malingering, tetanus, meningitis, encephalitis and poisoning and, in the paralytic type, other paralyses, e.g. Landry's, may have to be excluded.

Post-mortem diagnosis may be made in man or dog by examination of the brain. Both impression and crushed

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by

Cerebral inoculations of mice should also be made. Webster (1942) recommends the following procedure:—

'A' : The brain of the suspected animal is emulsified by grinding it in a mortar and injected in 2 to 3-weeks-old mice.

If the suspected material really contains rabies virus the mice usually develop Negri bodies on the 5th or 6th days, become sick on the 7th to 10th days, and die on the 9th to 12th days. They are generally uniform in their response—either nearly all become sick and die or all remain well. Rarely do the mice remain well for periods of 15 days and then develop rabies.

Great care should be taken to avoid self infection while carrying out these examinations.

Whenever possible expert advice should be obtained and if examination is to be carried out elsewhere the whole brain in the case of man and the whole head in the case of the dog should be sent in a suitable receptacle to the laboratory on ice—not on dry ice

## PREVENTION

**Control of rabies in animals**—This is first a matter of wise legislation and then rigid enforcement of the laws made. Six months quarantine for imported dogs, the licensing of all dogs and the destruction of all stray (unlicensed) dogs and the muzzling of all dogs while at large or in a public place whenever there is a rabies epizootic have successfully controlled this disease in several countries. Compulsory inoculation of dogs has also been adopted with success. It may be necessary to maintain these control measures over long periods and some of them of course permanently especially when there is a danger of reintroduction of infection by wild carnivores but rabies is an essentially controllable disease and should be controlled.

**Control of the infection in man**—When an individual is bitten by a dog that is known or suspected to be rabid the wound should be cleaned immediately and cauterized. After protecting the skin with vaseline this may be done carefully with fuming nitric acid or pure phenol which should be washed out with sterile saline. powdered potassium permanganate can also be used. The extent of the cauterization must depend on the site of the bite and on the chance of the dog's being rabid. While it must be admitted that unsightly scars have often been produced unnecessarily there is considerable evidence that skillful cauterization is of value. Cauterization must not be used as an excuse for neglecting anti rabies vaccination.

Anti rabies vaccination should be carried out as early as possible in every case of effective bite by a dog which is known to be rabid. Before this step is taken a determined effort to find out whether or not the animal was rabid should be made. When it can be caught it should be shut up and kept under observation and if it dies within 10 days or shows obvious signs of rabies and has to be destroyed the brain must be examined or sent for examination for evidence of rabies. If it survives this period it may be assumed that it was not rabid.

**The rabid animal**—The first evidence is a departure from normal behaviour and disposition. An unusual display of affection or the reverse or withdrawal from human and canine company irritability and snappishness should arouse suspicion. Later the animal will often run amok biting

Many febrile conditions such as distemper will cause cerebral symptoms especially in the young dog. These symptoms may include irrational behaviour with apparent aural and visual hallucinations which will often simulate rabies.

The virus is present in the salivary glands of a dog 3 to 4 days before it shows evidence of rabies.



**Indications for vaccination**—Whether anti rabie vaccination is begun immediately or whether a report on the dog is awaited will depend on circumstances the probability of the dogs being rabid and on the nature and location of the bite. In the case of severe bites on the upper limb and face treatment should be begun immediately if there was any possibility that the animal was rabid the same applies to any effective bite if there is strong evidence that the animal was rabid. On the other hand if the animal is under observation and the bite is a slight one through clothes or on the trunk or lower limbs it will be safe to await the verdict on the condition of the dog. Further when a dog under observation is declared non rabid any course of treatment commenced can be discontinued.

The virus does not enter through the unbroken skin so that licks and other contact with rabid animals are not an indication for anti rabie vaccination. It is however, the practice in most Pasteur institutes in India

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**Anti rabie vaccination**—Many types of vaccine both dead and alive have been used. There is considerable evidence that the best and most economical to prepare on a large scale is phenolized sheep vaccine made up as a 1 per cent emulsion of sheep's brain. It is given subcutaneously in doses of 5 c cm daily for 14 days. During the course of injections the patient is advised to take only light exercise and to avoid alcohol.

The only post vaccinal accident other than the avoidable ones due to sepsis is paralysis varying from that of a localized group of muscles to an ascending paralysis of the Landry type. This sequel only occurs in about one in ten thousand cases when killed vaccine is used although more frequently with live vaccine. The difference suggests that many of the latter cases are examples of fixed virus rabies. It is very rarely fatal.

#### TREATMENT

No specific treatment of the slightest value has yet been discovered.

The patient should be put to bed in a darkened room protected from all external stimuli and kept under the influence of sedatives and anti spasmodics of the latter the classical one is atropin. Sedatives must be administered in particularly large doses if they are to produce their effect.

#### PROGNOSIS

Experience indicates that once symptoms have developed the infection cannot be overcome and a fatal issue is inevitable. It must however be appreciated that there are many factors namely the position\* and depth of the bite the genus of the biter (jackal bites are more frequently fatal

\*The importance of this factor is well brought out in a recent report of the Pasteur Institute of Bengal attached to the Calcutta School of Tropical Medicine an analysis of the Indian patients who underwent treatment during 1939 shows the following—

Position of Bite	Number Treated	Deaths	Death Rate
Leg	3,203	12	0.375
Trunk	164	0	—
Arm	1,877	16	0.85
Head	250	11	4.40

than dog bites), the interposition of clothing, and the infectivity of the bite, to be taken into account, and it has been diversely estimated by different observers that from 2 to 80 per cent of all persons actually bitten by rabid animals, if untreated, would develop the disease. The present opinion is that the figure is about 10 per cent, and that efficient anti-rabies treatment will reduce the death rate in these persons, as a group, to about 1 per cent, but here yet another variable factor comes in, the time after the bite at which treatment is given. Most Pasteur institutes give a low death rate than this, but their figures are usually diluted by a large number of persons who were not bitten at all or who were bitten by non-rabid animals.

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## A NOTE ON MYIASIS AND SCARABIASIS\*

### MYIASIS

At times, invasion of the tissues and organs of man and other animals by fly maggots may take place. This condition is comprehensively known as myiasis.

The screw-worm larvæ of *Chrysomya bezziana* will infest the natural orifices of the human body, such as the ear, mouth, eye, nose, and vagina and cause considerable destruction of tissues. Myiasis due to *Cochliomya hominivorax* is common in man in tropical America.

The flesh-fly, *Sarcophaga*, generally causes external myiasis. The larvæ are deposited on gangrenous sores, lacerated wounds, etc. and being saprophagous in their habits they bring about a rapid healing of the ulcers. Larvæ of *Sarcophaga* sp., and successfully employed in the treatment of ulcers, whereas in America larvæ of *phora erythrocephala* grown in artificial maggot therapy.

Cutaneous myiasis is often caused by larvæ of bot-flies, subcutaneous tumours are generally produced. The maggots of sheep bot-flies *Oestrus ovis* have been found in the conjunctiva and nasal cavities of man in the Central Sahara in the United States and elsewhere.

Intestinal myiasis is to a great extent accidental, the larvæ being swallowed with food. The frequency with which 'rat-tailed' larvæ of the drone fly, *Eristalis tenax*, occur in liquid excrement should make one extremely cautious in accepting the numerous reports of these larvæ being evacuated with the stools. There are, however, several cases on record in which untoward symptoms such as indigestion, constipation, emaciation and dysentery could be associated with these larvæ in the intestine.

### SCARABIASIS

by the invasion of the intestine  
report children. It has not been re-  
their teeth and are able to cut out the affected  
Only those who have cut

The reports usually state that the insects are passed with the faeces at some months. The passing of the beetles  
ptoms of failing health such as loss of  
dysentery, progressive emaciation and  
temperature. The stool is usually semi-

\* By Dr D N Roy MD Professor of Entomology Calcutta School of Tropical Medicine

solid never hard, and after it has been voided, the attention of the mother is attracted to some movement in it a beetle gradually works its way to the surface, emerges and flies away. As a rule the infestation is by more than one beetle and sometimes over a period of months large numbers pass. The health of the child improves in the intervals. Strickland and Roy (1939) have discussed at length the method by which these insects gain access to the alimentary canal and they believe that the infestation takes place *per anum*.

Instances have been reported from the eastern parts of India, Ceylon also from South Africa.

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